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SEARCH REQUEST FORM

Date: 2/1/00 Requester's Full Name: DAVID LUKTON Examiner #: 71263
Art Unit: 1653 Phone (308) 3213 Serial Number: 08/930 584
Results Format Preferred (circle): (PAPER) DISK E-MAIL

****

Title of application: Biologically active peptides and compositions, their use

Inventors: ANDERSEN, RAYMOND; COLEMAN, JOHN; DE SILVA, DILIP; KONG, FANGMING; PIERS, EDWARD; WALLACE, DEBRA; ROBERGE, MICHEL; ALLEN, THERESA

Earliest priority date: 4/20/95

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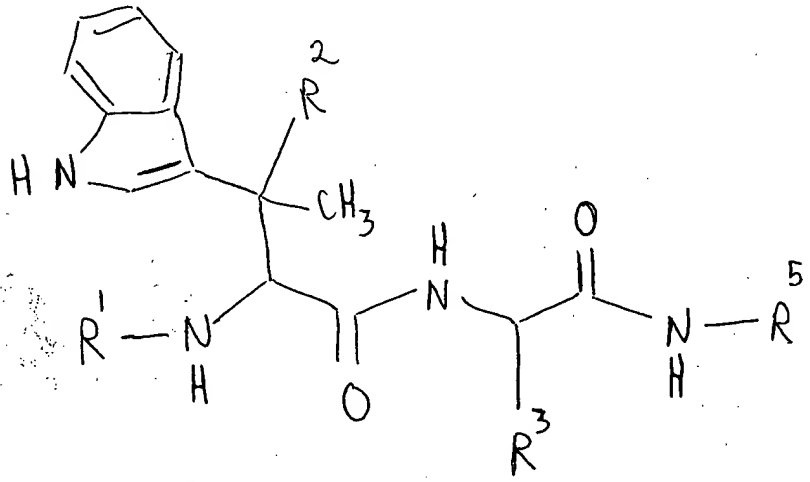
I would like to find references that disclose the following compounds.

R^1, R^3, and R^5 can be anything

R^2 is hydrogen or methyl

If there are several such disclosures, I would like to find one that teaches treatment of cancer (or tumors).



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Searcher Phone #: 308-4499
Searcher Location: _____
Date Searcher Picked Up: _____
Date Completed: 2/7/00
Searcher Prep & Review Time: _____
Online Time: _____

Type of Search
_____ NA Sequence (#)
_____ AA Sequence (#)
_____ Structure (#)
_____ Bibliographic
_____ Litigation
_____ Fulltext
_____ Other

Vendors and Cost
_____ STN _____ Dialog
_____ Questel/Orbit _____ Dr.Link
_____ Lexis/Nexis _____ Westlaw
_____ WWW/Internet
_____ In-house sequence systems (list)
_____ Other (specify)

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ACCESS DB # 24745 Location (Bldg/Room#): 9B05 10C01

Scientific and Technical Information Center

SEARCH REQUEST FORM

Date: 2/1/00 Requester's Full Name: DAVID LUKTON Examiner #: 71263

Art Unit: 1653 Phone (308) 3213 Serial Number: 08/930584

Results Format Preferred (circle): (PAPER) DISK E-MAIL

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To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of application: Biologically active peptides and compositions, their use

Inventors: ANDERSEN, RAYMOND; COLEMAN, JOHN; DE SILVA, DILIP; KONG, FANGMING; PIERS, EDWARD; WALLACE, DEBRA; ROBERGE, MICHEL; ALLEN, THERESA

Earliest priority date: 4/20/95

****

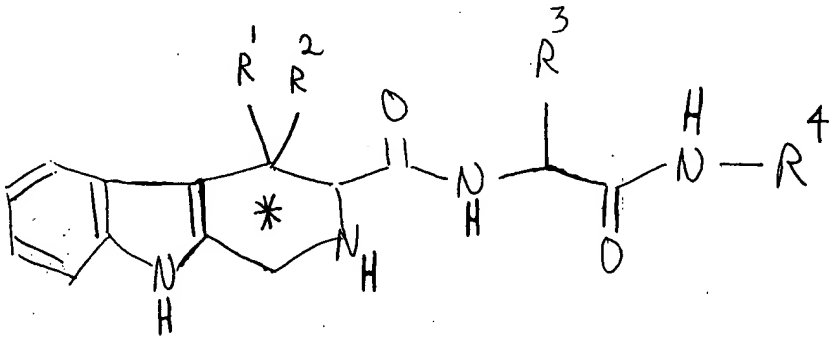
I would like to find references that disclose the compounds below.

R^1, and R^2 are independently hydrogen or alkyl;

R^3 and R^4 can be anything.

Alternatively, the ring containing the asterisk ("*") can be aromatic.

If there are several such disclosures, I would like to find one that teaches treatment of cancer (or tumors).



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Searcher Phone #: 308-4499

Searcher Location: _____

Date Searcher Picked Up: _____

Date Completed: 2/4/00

Searcher Prep & Review Time: _____

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Type of Search

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_____ AA Sequence (#)

_____ Structure (#)

_____ Bibliographic

_____ Litigation

_____ Fulltext

_____ Other

Vendors and Cost

_____ STN _____ Dialog

_____ Questel/Orbit _____ Dr.Link

_____ Lexis/Nexis _____ Westlaw

_____ WWW/Internet

_____ In-house sequence systems (list)

_____ Other (specify)

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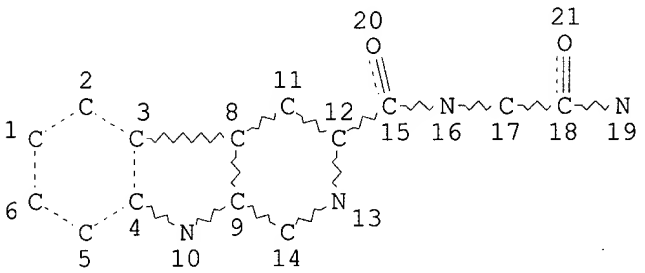

NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE
L5 195 SEA FILE=REGISTRY SSS FUL L1
L6 72 SEA FILE=HCAPLUS ABB=ON PLU=ON L5
L7 27 SEA FILE=HCAPLUS ABB=ON PLU=ON L6(L)(?CANCER? OR ?TUMOR? OR ?NEOPLAS?)

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=> d ibib abs hitrn l7 1-27

L7 ANSWER 1 OF 27 HCAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1999:559428 HCAPLUS
DOCUMENT NUMBER: 131:194602
TITLE: Growth inhibition of experimental pancreatic cancers and sustained reduction in epidermal growth factor receptors during therapy with hormonal peptide analogs
AUTHOR(S): Szepeshazi, Karoly; Halmos, Gabor; Schally, Andrew V.; Arencibia, Jose M.; Groot, Kate; Vadillo-Buenfil, Manuel; Rodriguez-Martin, Eulalia
CORPORATE SOURCE: Endocrine, Polypeptide Cancer Inst., VA Med. Center, New Orleans, LA, 70112, USA
SOURCE: J. Cancer Res. Clin. Oncol. (1999), 125(8/9), 444-452
CODEN: JCROD7; ISSN: 0171-5216
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In view of tumor growth inhibition epidermal growth factor (EGF) receptor redn. was studied in cancers. Hamsters with nitrosamine-induced pancreatic cancers were treated for 8 wk with bombesin/gastrin-releasing peptide (GRP) antagonist RC-3095, somatostatin analog RC-160, or the LH-releasing hormone antagonist cetrorelix by sustained delivery systems releasing 20, 35, and 20 .mu.g/day, resp. RC-3095 or cetrorelix resulted in an early (day 10) and sustained redn. (71% or 69%, resp.) on pancreatic tumors. RC-160 showed a 60% decrease only after 20 days. Histol. the decrease in argyrophilic nucleolar organizer regions showed a correlation with receptor redn. The concn. returned to control level 4 days after RC-3095 cessation. RC-160 single injection decreased receptors on pancreatic cancers by 31% 3 h after administration, returning to normal at 6 h. RC-3095 and cetrorelix single injections caused a 67% and 59% decline, resp., only 6 h after injection and the concn. remained low for 24 h.

IT **138147-78-1**, RC-3095
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(growth inhibition of pancreatic **cancers** and sustained redn. in EGF receptors during hormonal peptide analog therapy)

L7 ANSWER 2 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:377735 HCAPLUS
DOCUMENT NUMBER: 129:144603
TITLE: Inhibition of growth of MDA-MB-231 human breast cancer xenografts in nude mice by bombesin/gastrin-releasing peptide (GRP) antagonists RC-3940-II and RC-3095
AUTHOR(S): Miyazaki, M.; Lamharzi, N.; Schally, A. V.; Halmos, G.; Szepeshazi, K.; Groot, K.; Cai, R. Z.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans' Affairs Medical Center, Tulane University School of Medicine, New Orleans, LA, 70146, USA
SOURCE: Eur. J. Cancer (1998), 34(5), 710-717
CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bombesin or gastrin-releasing peptide (GRP) may act as autocrine growth factors and play a role in the initiation and progression of breast cancer. We investigated the effect of bombesin/GRP antagonists RC-3095 and RC-3940-II on the growth of the MDA-MB-231 estrogen-independent human breast cancer cell line xenografted into female nude mice. Bombesin/GRP antagonists, RC-3095 and RC-3940-II, were administered s.c. twice daily at a dose of 10 .mu.g for 5 wk. The growth of MDA-MB-231 tumors was inhibited during the treatment, as shown by a redn. in tumor vol. RC-3940-II and RC-3095 significantly decreased the final tumor vol. by 72.4% and 57.7%, resp., and greatly reduced tumor wts. RC-3940-II also significantly increased tumor doubling time and appeared to be more effective than RC-3095 in inhibiting the growth of MDA-MB-231 breast cancers. Serum gastrin and insulin-like growth factor-I (IGF-I) levels in animals treated with RC-3095 or RC-3940-II showed no significant changes

as compared with controls. There was a significant decrease in the no. of binding sites for epidermal growth factor (EGF), as well as bombesin, in tumor cells after chronic treatment with RC-3095 or RC-3940-II, which might be related to inhibition of tumor growth. Reverse transcription polymerase chain reaction, followed by Southern blot anal., also showed a redn. in the expression of mRNA for EGF receptors in the group treated with RC-3940-II. Our findings suggest that bombesin/GRP antagonists such as RC-3095 or RC-3940-II could be considered for endocrine therapy for estrogen-independent breast cancers, but further investigations are necessary.

IT **138147-78-1**, RC-3095
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of human breast **cancer** xenografts in nude mice by bombesin/gastrin-releasing peptide (GRP) antagonists RC-3940-II and RC-3095)

L7 ANSWER 3 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:634427 HCAPLUS
DOCUMENT NUMBER: 127:314475
TITLE: A single in vivo administration of bombesin antagonist RC-3095 reduces the levels and mRNA expression of epidermal growth factor receptors in MXT mouse mammary cancers
AUTHOR(S): Szepeshazi, Karoly; Schally, Andrew V.; Halmos, Gabor; Lamharzi, Najib; Groot, Kate; Horvath, Judit E.
CORPORATE SOURCE: Veterans Affairs Medical Center, Endocrine, Polypeptide Cancer Institute, Tulane University School Medicine, New Orleans, LA, 70146, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1997), 94(20), 10913-10918
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Epidermal growth factor (EGF) and its receptors (EGFR) play important roles in tumorigenesis. In various exptl. cancers, treatment with antagonists of bombesin/gastrin-releasing peptide (BN/GRP) produces a redn. in EGFRs, concomitant to inhibition of tumor growth. To investigate the mechanisms involved, we monitored concns. of BN/GRP antagonist RC-3095 in serum of mice, rats, and hamsters given a single s.c. or i.v. injection of this analog. In parallel studies, we measured levels and mRNA expression of EGFRs in estrogen-dependent and independent MXT mouse mammary cancers, following a single s.c. administration of RC-3095 to tumor-bearing mice. Peak values of RC-3095 in serum was detected 2 min after i.v. or 15 min after s.c. injection. The levels of RC-3095 declined rapidly and became undetectable after 3-5 h. In the estrogen-dependent MXT tumors, the concn. of EGF receptors was reduced by about 60% 6 h following injection and returned to original level after 24 h. Levels of mRNA for EGFR fell parallel with the receptor no. and were nearly normal after 24 h. In the hormone-independent MXT cancers, the no. of EGFRs decreased progressively, becoming undetectable 6 h after injection of RC-3095, and returned to normal values at 24 h, but EGFR mRNA levels remained lower for 48 h. Thus, in spite of rapid elimination from serum, BN/GRP antagonist RC-3095 can induce a prolonged decrease in levels and mRNA expression of EGFRs. These findings may explain how single daily injections of BN/GRP antagonists can maintain tumor growth inhibition.

IT **138147-78-1**, RC-3095
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(a single in vivo administration of bombesin antagonist RC-3095 reduces the levels and mRNA expression of epidermal growth factor receptors in MXT mouse mammary **cancers**)

L7 ANSWER 4 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:107924 HCAPLUS

DOCUMENT NUMBER: 126:246412
TITLE: Reduction in receptors for bombesin and epidermal growth factor in xenografts of human small-cell lung cancer after treatment with bombesin antagonist RC-3095
AUTHOR(S): Halmos, Gabor; Schally, Andrew V.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institure, Veterans Affairs Medical Center, New Orleans, LA, 70146, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1997), 94(3), 956-960
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Antagonists of bombesin/gastrin-releasing peptide (BN/GRP) have been developed to inhibit the stimulatory effects of BN/GRP on the mitogenesis of tumor cells such as human small-cell lung carcinoma (SCLC). The mode of action of these antagonists is not completely understood. In this study, the authors evaluated the effect of BN/GRP antagonist RC-3095 on receptors for BN/GRP and epidermal growth factor (EGF) in H-128 human SCLC line xenografted into nude mice. Treatment with RC-3095, administered s.c. at a dose of 20 .mu.g/day per animal for 4 wk caused a 70% redn. in tumor vol. and wt. Membrane receptors for BN/GRP and EGF were characterized in untreated and treated animals. In the control group, [125I-Tyr4]BN was bound to a single class of specific, high affinity binding sites with a dissocn. const. (Kd) = 6.55 nM and maximal binding capacity (Bmax) = 512.8 fmol/mg membrane protein. Therapy with RC-3095 decreased the concn. of BN/GRP receptors on H-128 SCLC tumor membranes. Specific, high affinity binding sites for EGF with Kd = 1.78 nM and Bmax = 216.8 fmol/mg membrane protein were also found on the untreated H-128 SCLC tumors. Treatment with RC-3095 significantly decreased Bmax of receptors for EGF. The results indicate that the suppression of growth of H-128 SCLC by BN antagonist RC-3095 is accompanied by a decrease in the no. of receptors for both BN/GRP and EGF. These observations are in agreement with the results obtained in other exptl. cancers. The findings on antagonist RC-3095 reinforce the view that both BN/GRP and EGF receptors participate in a cascade of events involved in the growth of SCLC and other cancers. Although the complete mechanisms of action of antagonist RC-3095 remain to be elucidated, the antitumor effect could be the result of the fall in the EGF receptor no., which might lead to a decrease in EGF receptor autophosphorylation.

IT **138147-78-1**, RC-3095
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(redn. in receptors for bombesin and epidermal growth factor in xenografts of human small-cell lung **cancer** after treatment with bombesin antagonist RC-3095)

L7 ANSWER 5 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:580851 HCAPLUS
DOCUMENT NUMBER: 125:237839
TITLE: Effects of new bombesin antagonists given singly or in combination with a somatostatin analog on nitrosamine-induced pancreatic cancers in hamsters
AUTHOR(S): Szepeshazi, Karoly; Schally, Andrew V.; Cai, Ren-Zhi; Halmos, Gabor; Groot, Kate
CORPORATE SOURCE: Veterans Affairs Medical Center, Polypeptide and Cancer Institute, New Orleans, LA, 70146, USA
SOURCE: Int. J. Oncol. (1996), 9(3), 397-403
CODEN: IJONES; ISSN: 1019-6439
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In three expts., hamsters with N-nitrosobis(2-oxopropyl)amine-induced pancreatic cancers were treated for two months with bombesin/GRP antagonists RC-3095 [D-Tpi6, Leu13.psi.(CH2NH)Leu14-bombesin(6-14)], RC-3910-II [D-Tpi6, Leu13.psi.(CH2N)Tac14-bombesin(6-14)], RC-3940-II [Hca6, Leu13.psi.(CH2N)Tac14-bombesin(6-14)], RC-3950-II [D-Phe6,

Leu13.psi.(CH2N)Tac14-bombesin(6-14)], somatostatin analog RC-160 (D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH2), or the combination of RC-3095 with RC-160. All peptides inhibited pancreatic cancers to various degrees, reducing the no. of tumorous animals, lowering the wt. of tumorous pancreata by 40-55% and decreasing AgNOR nos. which are indicators of cell proliferation rate. Combination therapy with RC-3095 and RC-160 did not inhibit tumors better than single peptides. Among new bombesin/GRP antagonists, RC-3940-II had the strongest inhibitory effect. RC-3950-II and RC-3095 caused similar inhibition, but RC-3910-II was less effective. Tumor inhibitory activity of the bombesin/GRP antagonists was correlated with their binding affinities to bombesin receptors on tumor cells. RC-3940-II caused 50% inhibition of specific binding of [125I=Tyr4]bombesin to tumor cell membranes at 0.96 nM concn., while the IC50 for RC-3950-II was 5.27 nM and 12.94 nM for RC-3095. Our findings suggest that in addn. to RC-3095, other bombesin/GRP antagonists such as RC-3950-II and esp. RC-3940-II could be further developed for therapy of human pancreatic cancer.

IT **138147-78-1**, RC-3095 **166774-43-2**, RC-3910-II
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of bombesin antagonists and somatostatin analog on pancreatic **cancers**)

L7 ANSWER 6 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:204166 HCAPLUS
DOCUMENT NUMBER: 124:283275
TITLE: Bombesin antagonist prevents CO2 laser-induced promotion of oral cancer
AUTHOR(S): Kozacko, Mark F.; Mang, Thomas S.; Schally, Andrew V.; Priore, Roger L.; Liebow, Charles
CORPORATE SOURCE: Department Oral Maxillofacial Surgery, State University New York, Buffalo, NY, 14214, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1996), 93(7), 2953-7
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We previously reported that CO2 laser incisions in carcinogen-initiated fields promoted cancer development and caused release of growth factors. Here we examd. the quant. and additive properties of this tumor-promoting event and examd. whether this promotion could be nullified by treatment with a bombesin antagonist, which down-regulates epidermal growth factor receptors. The model used for cancer promotion was the hamster buccal cheek pouch that had been treated with a carcinogen (9,10-dimethyl-1,2-benzanthracene) for 6 wk, producing premalignant lesions. These lesions would evolve into a cancer eventually without further treatment. Promotion was measured both by increased fluorescence in response to systemically administered Photofrin, measured noninvasively using an in vivo fluorescence photometer, and by the timing of appearance of clin. tumors. Laser incisions (0-3) were made into the hamster cheek 1 wk apart, or three incisions were done 1 day apart. Another group of animals received bombesin antagonist RC-3095 for 4 wk during the time incisions were made, again measuring promotion. Laser incisions 1 wk apart produced additive promotion, whereas three incisions 1 day apart were not statistically different from the group receiving only one incision. RC-3095 treatment completely eliminated the promoting effects of incision and totally stopped promotion for the 4-wk period of treatment. After discontinuing treatment with RC-3095, lesion progression resumed at the untreated control rate. This work confirms that the promoting event of a laser incision follows a comparable time course to release of growth factors after such an incision and that it can be eliminated by treatment with bombesin antagonists.

IT **138147-78-1**, RC-3095
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bombesin antagonist prevents CO2 laser-induced promotion of oral **cancer**)

L7 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:670803 HCAPLUS
DOCUMENT NUMBER: 123:131996
TITLE: New pseudononapeptide bombesin antagonists with C-terminal Leu.psi.(CH2N)Tac-NH2 show high binding affinity to bombesin/GRP receptors on CFPAC-1 human pancreatic cancer cells
AUTHOR(S): Cai, Ren-Zhi; Qin, Yunfeng; Ertl, Tibor; Schally, Andrew V.
CORPORATE SOURCE: Veterans Affairs Medical Center, Endocrine, Polypeptide and Cancer Institute, New Orleans, LA, USA
SOURCE: Int. J. Oncol. (1995), 6(6), 1165-72
CODEN: IJONES; ISSN: 1019-6439
DOCUMENT TYPE: Journal
LANGUAGE: English
AB It has been demonstrated that bombesin/GRP antagonist D-Tpi6,Leu13.psi.(CH2NH) Leu14-BN(6-14) (RC-3095) inhibits effectively the growth of pancreatic cancer and other tumors in exptl. animals and in cell cultures. In an attempt to develop antagonists with still greater antitumor activity, several new pseudononapeptide bombesin/GRP antagonists contg. C-terminal Leu.psi.(CH2N)Tac-NH2 have been synthesized in our lab. In this study, we investigated the ability of four Leu13.psi.(CH2N)Tac14-BN(6-14) antagonists to inhibit the binding of bombesin to specific receptors for bombesin/GRP on CFPAC-1 human pancreatic cancer cells. Receptor binding assays were performed by incubating CFPAC-1 cells (5.times.104 cells/well) with 0.5 nM [125I]-Tyr4-bombesin in the absence or presence of (1 pM to 10 .mu.M) unlabeled bombesin, GRP (14-27) and various antagonists for 2 h at 22.degree.C. Displacement assays showed that antagonist D-Tpi6,Leu13.psi.(CH2N)Tac14-BN(6-14) (RC-3910-II) with a similar structure to RC-3095, but a different C-terminal, had a binding affinity to CFPAC-1 cells 15 times higher than RC-3095. Three other antagonists, RC-3925-II, RC-3940-II and RC-3950-II contained the same C-terminal Leu.psi.(CH2N)Tac-NH2 as RC-3910-II, but had different N-terminal residues: D-Cpa, Hca and D-Phe, resp. Among them, Hca6,Leu13.psi.(CH2N)Tac14-BN(6-14) (RC-3940-II) showed the highest binding affinity to the receptors on CFPAC-1 cells, which was 50 times higher than that of RC-3095 or 3 times greater than RC-3910-II. Our findings suggest the merit of further investigation of pseudononapeptide bombesin/GRP antagonist RC-3940-II and related analogs for a possible development of a new hormonal therapy for pancreatic cancer.
IT **138147-78-1**, RC-3095 **166774-43-2**, RC 3910-II
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new pseudononapeptide bombesin antagonists with C-terminal Leu.psi.(CH2N)Tac-NH2 show high binding affinity to bombesin/GRP receptors on CFPAC-1 human pancreatic **cancer** cells)

L7 ANSWER 8 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:633574 HCAPLUS
DOCUMENT NUMBER: 123:48011
TITLE: Development of a radioimmunoassay for a pseudononapeptide bombesin/GRP antagonist with antitumor activity
AUTHOR(S): Groot, Kate; Horvath, Judit E.; Cai, Ren-Zhi; Schally, Andrew V.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Inst., Veterans Affairs Medical Center, New Orleans, LA, USA
SOURCE: Int. J. Pept. Protein Res. (1995), 45(6), 561-6
CODEN: IJPPC3; ISSN: 0367-8377
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Bombesin-like and GRP-like peptides may act as autocrine growth factors in the proliferation of some cancers. A pseudononapeptide bombesin antagonist, [D-Trp6,Leu13.psi.(CH2NH)-Leu14]bombesin(6-14), and related analogs synthesized in the lab. significantly inhibit tumor growth in

various cancer models. A RIA, suitable for detn. of RC-3095 and its congeners in unextd. serum, was developed to facilitate further exptl. and clin. evaluation of this bombesin/GRP receptor antagonist for the treatment of various tumors. Antibodies were generated against RC-3095 and Des-Tpi1-RC-3095, conjugated to bovine serum albumin with glutaraldehyde. Antiserum JH-631b was selected for further expts. based on the antibody characterization. At an antiserum diln. of 1:189,000, this antibody bound .apprx.50% of 7 fmol of added radiolabeled Tyr1-RC-3095. The antibody cross-reacted with C-terminal fragments of RC-3095. Fragments without the C-terminus and naturally existing peptides of the bombesin family or structurally unrelated peptides did not cross-react. The min. detectable dose of RC-3095 was 0.4 pg/tube. Intra- and interassay coeffs. of variation ranged from 3.2 to 4.4% and from 5.6 to 12.8%, resp. The RIA is suitable for direct detn. of RC-3095 in serum. The RIA should be of value for monitoring levels of this analog in serum during long-term therapy.

IT **138147-78-1**, RC 3095
RL: ANT (Analyte); ANST (Analytical study)
(RIA of blood serum content of pseudononapeptide bombesin/GRP antagonist with **antitumor** activity)

L7 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:432974 HCAPLUS
DOCUMENT NUMBER: 122:255644
TITLE: Inhibitory effect of bombesin/gastrin-releasing peptide (GRP) antagonists RC-3950-II and RC-3095 on MCF-7 MIII human breast cancer xenografts in nude mice
AUTHOR(S): Shirahige, Y; Cai, R-Z; Szepeshazi, K; Halmos, G; Pinski, J; Groot, K; Schally, AV
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, New Orleans, LA, 70146, USA
SOURCE: Biomed. Pharmacother. (1994), 48(10), 465-72
CODEN: BIPHEX; ISSN: 0753-3322
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bombesin/gastrin-releasing peptide (GRP) may be involved in the growth of human breast cancers. Nude mice bearing xenografts of MCF-7 MIII human breast cancer cell line were treated for 7 wk with bombesin/GRP antagonists RC-3950-II and RC-3095. RC-3950-II, administered s.c. twice daily at a dose of 10 .mu.g, produced significant inhibitory effects on tumor growth after 2 wk of administration. RC-3095 acetate (D 22213), injected s.c. twice daily at the same dose of 10 .mu.g, suppressed tumor growth after 4 wk. Both RC-3950-II and RC-3095 significantly decreased the final tumor vol. and tumor wts. RC-3950-II appeared to be somewhat more efficacious than RC-3095 in inhibiting the growth of MCF-7 MIII breast cancers. Chronic treatment with either bombesin/GRP antagonist caused downregulation of receptors for epidermal growth factor (EGF) in tumor cell membranes, which might be related to inhibition of tumor growth. These findings suggest that bombesin/GRP antagonists should be considered for a new endocrine therapy of breast cancer.

IT **138147-78-1**, RC-3095 **162666-31-1**, D 22213
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antitumor** effect of bombesin/gastrin-releasing peptide antagonists RC-3950-II and RC-3095 on human breast **cancer**)

L7 ANSWER 10 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:401389 HCAPLUS
DOCUMENT NUMBER: 122:177845
TITLE: Bombesin antagonists inhibit in vitro and in vivo growth of human gastric cancer and binding of bombesin to its receptors
AUTHOR(S): Qin, Yunfeng; Halmos, Gabor; Cai, Ren-Zhi; Szoke, Balazs; Ertl, Tibor; Schally, Andrew V.
CORPORATE SOURCE: Veterans Affairs Medical Center, Endocrine Polypeptide and Cancer Institute, New Orleans, LA, 70146, USA
SOURCE: J. Cancer Res. Clin. Oncol. (1994), 120(9), 519-28

CODEN: JCROD7; ISSN: 0171-5216
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We investigated the effect of bombesin/gastrin releasing peptide (GRP) antagonist RC-3095 and other analogs on the growth of Hs746T human gastric cancer cells implanted in nude mice or cultured in vitro and on the binding of bombesin to its receptors. Nude mice bearing xenografts of the Hs746T cell line received s.c. injections of RC-3095 (10 .mu.g twice daily) or the vehicle (control) for 21 days. Administration of antagonist RC-3095 inhibited the growth of Hs746T tumors. Treatment with RC-3095 produced a significant decrease in tumor vol., prolonged the tumor vol. doubling time from 3.6 days to 5.1 days, and decreased the tumor growth rate by 76.9%. The tumor growth delay time in mice treated with RC-3095 was 2.8 days. Treatment with RC-3095 also decreased the final tumor wt. by 88.3% and reduced DNA and protein contents in tumors by 91.5% and 89.5%, resp., as compared to controls. The presence of specific receptors for bombesin/GRP was investigated on the crude membranes of implanted tumors of Hs746T cells. Satn. binding assays showed that the binding of [125I-Tyr4]bombesin to the membranes was saturable and reversible. Scatchard anal. indicated the presence of a single class of binding sites with a high affinity (Kd = 0.24 .+-. 0.07 nM) and a low binding capacity (Bmax = 57.0 .+-. 0.9 fmol/mg protein). In displacement studies, the binding of [125I-Tyr4]bombesin was inhibited in a dose-dependent manner by unlabeled bombesin(1-14), [Tyr4]-bombesin and GRP (14-27), but not by structurally unrelated peptides. Synthetic bombesin/GRP antagonists RC-3095, RC-3110, and RC-3950-II were all able to inhibit effectively the binding of [125I-Tyr4]bombesin to the membranes of Hs746T cells. RC-3950-II showed a higher binding affinity for bombesin receptors than RC-3095 or RC-3110. Addn. of the non-hydrolyzable guanine-nucleotide analog GTP [S] to the binding buffer caused a significant redn. in the amt. of [125I-Tyr4]bombesin bound to the cells, indicating that the bombesin receptor is coupled to a G-protein. In cell cultures, bombesin significantly stimulated the growth of Hs746T cells in vitro as shown by an increase in the uptake of [3H]thymidine. Bombesin antagonist RC-3095 could effectively inhibit the bombesin-stimulated growth of Hs746T cells in cultures. These observations suggest that bombesin/GRP may act as growth factors through specific receptors present on the membranes of Hs746T cells. Bombesin/GRP antagonists appear to nullify the effects of bombesin/GRP and may be useful for the treatment of gastric cancers.

IT **138147-78-1**, RC-3095
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bombesin antagonist RC-3095 inhibition of human gastric **cancer** growth and bombesin binding to its receptors)

L7 ANSWER 11 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:278612 HCAPLUS
DOCUMENT NUMBER: 123:9930
TITLE: Polypeptide bombesin antagonists
INVENTOR(S): Schally, Andrew V.; Cai, Renzhi
PATENT ASSIGNEE(S): The Administrators of the Tulane Educational Fund, USA
SOURCE: U.S., 36 pp. Cont.-in-part of U.S. 5,244,883.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5369094	A	19941129	US 1993-31325	19930315
US 5244883	A	19930914	US 1990-619747	19901129
CA 2097192	AA	19920530	CA 1991-2097192	19911115
HU 64566	A2	19940128	HU 1993-1567	19911115
HU 213114	B	19970228		
AT 120760	E	19950415	AT 1992-900740	19911115

ES 2072137	T3	19950701	ES 1992-900740	19911115
ZA 9109387	A	19920930	ZA 1991-9387	19911128
WO 9421674	A1	19940929	WO 1994-US2511	19940307
W: AU, BR, BY, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SI, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2135787	AA	19940929	CA 1994-2135787	19940307
CA 2157871	AA	19940929	CA 1994-2157871	19940307
AU 9464446	A1	19941011	AU 1994-64446	19940307
AU 666270	B2	19960201		
EP 646127	A1	19950405	EP 1994-912199	19940307
EP 646127	B1	19980701		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07507330	T2	19950810	JP 1994-521091	19940307
HU 69727	A2	19950928	HU 1994-3244	19940307
AT 167874	E	19980715	AT 1994-912199	19940307
ES 2120615	T3	19981101	ES 1994-912199	19940307
ZA 9401767	A	19941006	ZA 1994-1767	19940314
NO 9404293	A	19950102	NO 1994-4293	19941110
FI 9405378	A	19941115	FI 1994-5378	19941115
PRIORITY APPLN. INFO.:			US 1990-619747	19901129
			US 1993-31325	19930315
			WO 1994-US2511	19940307

OTHER SOURCE(S): MARPAT 123:9930

AB Pseudopeptides comprising a peptide of formula I: X-A1-A2-Trp-Ala-Val-Gly-His-Leu-.psi.-A9-Q wherein X is hydrogen, a single bond linking the .alpha. amino group of A1 to the .gamma. carboxyl moiety on the 3-propionyl moiety of A2 when A2 is Glu, or a group of formula R1CO wherein R1 is selected from the groups consisting of:. (A) hydrogen, C1-10-alkyl, Ph or phenyl-C1-10-alkyl, p-HI-Ph, p-HI-phenyl-C1-10-alkyl, naphthyl, naphthyl-C1-10-alkyl, indolyl, indolyl-C1-10-alkyl, pyridyl, pyridyl-C1-10-alkyl, thienyl, thienyl-C1-10-alkyl, cyclohexyl or cyclohexyl-C1-10-alkyl, where HI = F, Cl, Br, OH, CH3 or OCH3;. (B) N(R2)(R3), wherein R2 is hydrogen, C1-10 alkyl, Ph or phenyl-C1-10-alkyl, R3 is hydrogen or C1-10 alkyl;. (C) R4O, wherein R4 is C1-10 alkyl, Ph or phenyl-C1-10 -alkyl; A1 is a D- or L- amino acid residue selected from the group consisting of Phe, p-HI-Phe, pGlu, Nal, Pal, Tpi, unsubstituted Trp or Trp substituted in the benzene ring by one or more members selected from the group consisting of F, Cl, Br, NH2 or C1-3 alkyl; or A1 is a peptide bond linking the acyl moiety of R1CO to the .alpha. amino moiety of A2 ; A2 is Gln, Glu[--], Glu(Y) or His, wherein [--] is a single bond linking the .gamma. carboxyl group of A2 when A2 is Glu with the .alpha. amino group of A1 where X is a single bond, Y is OR5 or N(R5)(R6) wherein R5 is hydrogen, C1-3 alkyl or phenyl; R6 is hydrogen or C1-3 alkyl; and R7 is hydrogen, C1-3 alkyl or NHCONH2 ; Leu-.psi. is a reduced form of Leu wherein the C:O moiety is instead CH2 such that the bond of this CH2 moiety with the .alpha. amino group of the adjacent A9 residue is a pseudopeptide bond; A9 is Tac, MTac or DMTac; and Q is NH2 or OQ1 where Q1 is hydrogen, C1-10 alkyl, Ph or phenyl-C1-10 -alkyl; and the pharmaceutically acceptable acids or salts thereof. Inhibition of binding of 125I-Tyr4-bombesin to Swiss 3T3 cells by bombesin antagonists: Ki (nM) from <0.001 to 213. The effects of treatment with bombesin antagonists on tumor vol. of estrogen independent MXT mouse mammary cancers, human small cell lung carcinoma in nude mice, MIA PACA-2 pancreatic cancer tumors, and CAPAN-2 human pancreatic cancer were also reported.

IT **143491-06-9P 163759-26-0P 163759-34-0P**
163759-38-4P 163878-59-9P 163878-60-2P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(polypeptide bombesin antagonists as **neoplasm** inhibitors)

IT **163759-36-2DP**, resin bound **163878-62-4DP**, resin bound
RL: SPN (Synthetic preparation); PREP (Preparation)
(polypeptide bombesin antagonists as **neoplasm** inhibitors)

L7 ANSWER 12 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:236063 HCAPLUS

DOCUMENT NUMBER: 122:122615
TITLE: Effects of somatostatin analog RC-160 and bombesin/gastrin-releasing peptide antagonists on the growth of human small-cell and non-small-cell lung carcinomas in nude mice
AUTHOR(S): Pinski, J.; Schally, A.V.; Halmos, G.; Szepeshazi, K.; Groot, K.; O'Byrne, K.; Cai, R.-Z.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, New Orleans, LA, 70146, USA
SOURCE: Br. J. Cancer (1994), 70(5), 886-92
CODEN: BJCAAI; ISSN: 0007-0920
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We investigated the effects of our synthetic bombesin/gastrin-releasing peptide (GRP) antagonists and somatostatin analog RC-160 on the growth of human small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (non-SCLC) lines in nude mice. Athymic nude mice bearing xenografts of the SCLC NCI-H69 line or non-SCLC NCI-H157 line were treated for 5 and 4 wk, resp., with somatostatin analog RC-160 or various bombesin/GRP antagonists. RC-160, administered s.c. peritumorally at a dose of 100 .mu.g per animal per day, inhibited the growth of H69 SCLC xenografts as shown by more than 70% redn. in tumor vols. and wts., as compared with the control group. Bombesin/GRP antagonists, RC-3440, RC-3095 and RC-3950-II, given s.c. peritumorally at a dose of 20 .mu.g per animal per day, also inhibited the growth of H69 SCLC tumors. RC-3950-II had the greatest inhibitory effect and decreased tumor vol. and wts. by more than 80%. The growth of H-157 non-SCLC xenografts was significantly reduced by treatment with RC-160, but not with bombesin/GRP antagonist RC-3095. In mice bearing either tumor model, administration of RC-160 significantly decreased serum growth hormone and gastrin levels. Specific high-affinity receptors for bombesin and somatostatin were found on membranes of SCLC H69 tumors, but not on non-SCLC H157 tumors. Receptor analyses demonstrated high-affinity binding sites for epidermal growth factor (EGF) and insulin-like growth factor I (IGF-I) on the membranes of H69 and H157 tumors. EGF receptors were down-regulated on H69 tumors after treatment with RC-160 and bombesin/GRP antagonists. The concn. of binding sites for EGF and IGF-I on the H157 tumors was decreased after treatment with RC-160, but bombesin/GRP antagonist RC-3095 had no effect. These results demonstrate that bombesin/GRP antagonists inhibit the growth of H-69 SCLC, but not of H-157 non-SCLC xenografts in nude mice, whereas somatostatin analog RC-160 is effective in both tumor models. This raises the possibility that these peptide analogs could be used selectively in the treatment of various subclasses of lung cancer.

IT **138147-78-1**, RC-3095 **142824-94-0**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(somatostatin analog RC-160 and bombesin/gastrin-releasing peptide antagonists RC-3440, RC-3095, and RC-3950-II **antitumor** effect on human small-cell and non-small-cell lung carcinoma)

L7 ANSWER 13 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:222483 HCAPLUS
DOCUMENT NUMBER: 122:24089
TITLE: Combination treatment of nitrosamine-induced pancreatic cancers in hamsters with analogs of LH-RH and a bombesin/GRP antagonist
AUTHOR(S): Szepeshazi, Karoly; Halmos, Gabor; Groot, Kate; Schally, Andrew V.
CORPORATE SOURCE: Endocrine, Polypeptide, and Cancer Institute, Veterans Affairs Medical Center, New Orleans, LA, 70146, USA
SOURCE: Int. J. Pancreatol. (1994), 16(2-3), 141-9
CODEN: IJPNEX; ISSN: 0169-4197
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Analogs of LH-releasing hormone (LH-RH) and bombesin/gastrin-releasing peptide were previously shown to inhibit the growth of exptl. pancreatic

cancers. In the present study, to increase the efficacy of therapy, female Syrian golden hamsters with N-nitrosobis(2-oxopropyl)amine-induced pancreatic cancers were treated for 2 mo with a combination of LH-RH agonist [D-Trp6]LH-RH or antagonist [Ac-D-Nal(2)1,D-Phe(4Cl)2,D-Pal(3)3,D-Cit6-Ala10]LH-RH (SB-75) and bombesin/GRP antagonist D-Tpi6,Leu13.psi.(CH2NH)Leu14bombesin(6-14) (RC-3095). The results were compared to those obtained by treatment with same doses of single peptides. LH-RH analogs and bombesin antagonist given alone significantly reduced the no. of tumorous animals and decreased wt. of pancreata by 46-71% and wt. of tumorous pancreas by 38-64%. Histol. showed lower mitotic activity and a decreased no. of AgNORs in tumor cells from treated animals. Enhanced apoptosis was also obsd. after treatment with the LH-RH analogs. Combination therapy had no superior inhibitory effect on tumors compared to single peptides, by practically all the parameters analyzed. The reasons for this lack of potentiation are not clear. The tumor inhibitory effect of bombesin antagonists appears to be mediated by interference with EGF-receptor mechanisms. In the present study, although a significant downregulation of EGF-receptors was found in tumors treated with combination, the decrease in binding capacity for EGF was maximal in the group treated with RC-3095 alone. Since intracellular signaling mechanisms are common for LH-RH and bombesin-like peptides, it is possible that second messengers were already maximally utilized by treatment with single peptides. Bombesin/GRP abolished the apoptosis enhancing effect of the LH-RH analogs, probably by interference in intracellular mechanisms. A more complete elucidation of the exact mechanisms of action of LH-RH and bombesin/GRP analogs is necessary for planning a successful combination therapy with these peptides.

IT **138147-78-1**, RC-3095
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pancreatic **cancer** treatment in hamsters with analogs of LH-RH and bombesin GRP antagonist)

L7 ANSWER 14 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:596444 HCAPLUS
DOCUMENT NUMBER: 121:196444
TITLE: Characterization of high-affinity receptors for bombesin/gastrin releasing peptide on the human prostate cancer cell lines PC-3 and DU-145: internalization of receptor bound 125I-[Tyr4]bombesin by tumor cells
AUTHOR(S): Reile, Herta; Armatis, Patricia E.; Schally, Andrew V.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, New Orleans, LA, 70146, USA
SOURCE: Prostate (N. Y.) (1994), 25(1), 29-38
CODEN: PRSTDS; ISSN: 0270-4137
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Specific receptors for bombesin/gastrin releasing peptide (GRP) on the androgen-independent human prostate cancer cell lines PC-3 and DU-145 were characterized. No specific binding of 125I-[Tyr4]bombesin to the androgen-dependent human prostate cancer cell line LNCaP was detectable. The binding of 125I-[Tyr4]bombesin to PC-3 and DU-145 cells was time- and temp.-dependent, saturable, and reversible. Scatchard anal. revealed a single class of binding sites with high affinity (Kd 9.8.times.10-11M for PC-3, and 9.1.times.10-11M for DU-145 cells at 25.degree.) and with a binding capacity of 44,000 binding sites/cell and 19,000 binding sites/cell, resp. Bound 125I-[Tyr4]bombesin was rapidly internalized by PC-3 cells. The nonhydrolyzable GTP analog GTP-.gamma.-S caused a dose-dependent inhibition of 125I-[Tyr4]bombesin binding to PC-3 and DU-145 cells, indicating that a G-protein couples the bombesin receptor to intracellular effector systems. Bombesin and GRP(14-27) inhibited the binding of 125I-[Tyr4]-bombesin to both cell lines in a dose-dependent manner with inhibition consts. (Ki) of 0.5 nM and 0.4 nM, resp. Both cell lines express the bombesin/GRP-preferring bombesin receptor subtype, since, in displacement studies, neuromedin B was >200-fold less potent than bombesin and GRP(14-27) in inhibiting the binding of

125I-[Tyr4]bombesin. Two synthetic bombesin/GRP antagonists, RC 3095 and RC 3110, powerfully inhibited the specific binding of 125I-[Tyr4]bombesin with Ki 0.92 nM and 0.26 nM on PC-3 cells, and 3.3 nM and 0.89 nM on DU-145 cells, resp. Apparently, the PC-3 and DU-145 human prostate cancer cell lines possess specific high-affinity receptors for bombesin/GRP, and are suitable models for the evaluation of the antineoplastic activity of new bombesin/GRP antagonists in the treatment of androgen-independent prostate cancer.

IT **138147-78-1**, RC 3095
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bombesin binding to human prostate **cancer** cell lines PC-3 and DU-145 inhibition by)

L7 ANSWER 15 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:474291 HCAPLUS
DOCUMENT NUMBER: 121:74291
TITLE: Characterization of a bombesin/gastrin-releasing peptide receptor on a human gastric-cancer cell line
AUTHOR(S): Preston, Shaun R.; Woodhouse, Linda F.; Gokhale, Jay; Miller, Glenn V.; Primrose, John N.
CORPORATE SOURCE: Academic Unit Surgery, St. James's University Hospital, Leeds, LS9 7TF, UK
SOURCE: Int. J. Cancer (1994), 57(5), 734-41
CODEN: IJCNAW; ISSN: 0020-7136
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study examd. the expression of receptors of the bombesin (BBS) family in human gastric-cancer cell lines. Of 5 cell lines screened, only one, St42, demonstrated specific binding sites for 125I-Tyr4-BBS, which have been further characterized. This binding was saturable, and temp.- and time-dependent. Scatchard anal. of displacement data performed at 37.degree. revealed 2 binding sites: a high-affinity, low-capacity site (KD = 0.13 nM, Bmax = 1500 sites/cell) and a lower-affinity, higher-capacity site (KD = 11 nM, Bmax = 35,000 sites/cell); the latter was lost when internalization of peptide was prevented, suggesting that it may be an artifact. Displacement assays with gastrin-releasing peptide (GRP) and neuromedin B (NMB) revealed that the receptor was of the GRP-preferring sub-type (GRP IC50 = 0.35 nM; NMB IC50 = 112 nM). Co-valent crosslinking of 125I-Tyr4-BBS to the receptor demonstrated the presence of a single band corresponding to a mol. wt. of 37 to 44 kDa on SDS-PAGE, similar to that of the cloned GRP receptor protein core. G-protein linkage of this receptor was demonstrated by selective inhibition of 125I-Tyr4-BBS binding by guanosine nucleotides. The binding of BBS to the receptor resulted in a rise in intracellular calcium. Three of four structurally distinct BBS antagonists bound to the receptor with high affinity, but [DPhe12, Leu14]-bombesin did not cause any displacement of 125I-Tyr4-BBS even at 10 mM. The functional significance of GRP receptors on human gastric-cancer cells is as yet unknown, but further studies may det. whether such receptors have importance in the therapy of gastric cancer.

IT **138147-78-1**, RC-3095
RL: BIOL (Biological study)
(gastrin-releasing peptide receptor affinity for, of human gastric **cancer** cells)

L7 ANSWER 16 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:450450 HCAPLUS
DOCUMENT NUMBER: 121:50450
TITLE: Inhibitory effect of bombesin/gastrin-releasing peptide antagonist RC-3095 and luteinizing hormone-releasing hormone antagonist SB-75 on the growth of MCF-7 MIII human breast cancer xenografts in athymic nude mice
AUTHOR(S): Yano, Tetsu; Pinski, Jacek; Szepeshazi, Karoly; Halmos, Gabor; Radulovic, Sinisa; Groot, Kate;

Schally, Andrew V.
CORPORATE SOURCE: Veterans Aff. Med. Cent., Endocr. Polypept. and Cancer Inst., New Orleans, LA, USA
SOURCE: Cancer (Philadelphia) (1994), 73(4), 1229-38
CODEN: CANCAR; ISSN: 0008-543X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The results of several clin. trials using various LH-releasing hormone agonists for treatment of advanced breast cancer are encouraging. However, only about 30% of breast cancers are estrogen-dependent and can be treated by hormonal manipulation. New therapeutic approaches combining estrogen ablation therapy with other compds. must be explored. Various studies suggest that bombesin or gastrin-releasing peptide acts as an autocrine growth factor and may play a role in the initiation and progression of some cancers, including that of the breast. Female athymic nude mice bearing xenografts of the MCF-7 MIII human breast cancer cell line were treated for 7 wk with bombesin/gastrin-releasing peptide antagonist (D-Tpi6, Leu13 .PSI.[CH2NH]-Leu14) bombesin (6-14) (RC-3095) injected s.c. daily at a dose of 20 .mu.g and LH-releasing hormone antagonist SB-75 (Cetrorelix) administered biweekly in the form of microgranules releasing 45 .mu.g/day. After 2 wk of treatment, a significant inhibition of tumor vol. was obsd. in the groups treated with RC-3095 alone or in combination with SB-75 but not in those treated with SB-75 as a single agent. After 7 wk, tumor growth as measured by tumor vol. and percentage changes in tumor vol. and tumor wt. was greatly inhibited in all of the treated groups. Uterine and ovarian wts. were reduced and serum LH levels decreased by administration of SB-75 alone or in combination with RC-3095. Histol., a significant decrease in argyrophilic nucleolar organizer region count in tumor cell nuclei was obsd. in all of the treated groups, indicating a lower proliferation of these cells. High-affinity binding sites for bombesin were detected in cultured MCF-7 MIII cells. Chronic treatment with RC-3095 caused a significant down-regulation of epidermal growth factor receptors in tumor cell membranes, which might be related to tumor inhibition. In studies in vitro, SB-75 inhibited proliferation of MCF-7 cells in culture but not proliferation of MCF-7 MIII cells. Because previously the authors demonstrated that RC-3095 inhibits the proliferation of MCF-7 MIII cells in vitro, it appears that the major antitumoral effect of RC-3095 on the MCF-7 MIII cancer line is direct, whereas that of SB-75 is indirect, and that it is mediated by suppression of the pituitary-gonadal axis. In view of its immediate and powerful inhibitory effect on MCF-7 MIII tumors, bombesin/gastrin-releasing peptide antagonist RC-3095 might be considered as a possible new agent for the treatment of breast cancer.
IT **138147-78-1**, RC-3095
RL: BIOL (Biological study)
(breast **cancer** of humans inhibition by, in lab. animals, LHRH antagonist SB-75 effect on)

L7 ANSWER 17 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:290486 HCAPLUS
DOCUMENT NUMBER: 120:290486
TITLE: Synergistic effects of bombesin and epidermal growth factor on cancers
AUTHOR(S): Liebow, Charles; Crean, David H.; Lee, Ming T.; Kamer, Angela R.; Mang, Thomas S.; Schally, Andrew V.
CORPORATE SOURCE: Buffalo Gen. Hosp., State Univ. New York, Buffalo, NY, 14214, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1994), 91(9), 3804-8
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Bombesin and gastrin-releasing peptide act as autocrine mitogens in various cancers. Bombesin antagonist RC-3095 inhibited growth in some cancers and slowed the progression of premalignant lesions, possibly by down-regulating epidermal growth factor (EGF) receptors. Since the EGF receptor mitogen response involves tyrosine kinase stimulation, the

authors tested the hypotheses that bombesin stimulates, and RC-3095 inhibits, phosphorylation; EGF and bombesin promote the phosphorylation of the same substrates; and EGF and bombesin act synergistically on phosphorylation. Therefore, in vitro assays for phosphorylation were performed in the presence of absence of EGF, bombesin, RC-3095, and combinations in samples derived from tumor, tissue surrounding tumor, cell lines, and normal and transforming tissue derived from the 9,10-dimethyl-1,2-benzanthracene-induced squamous cell lesions of the hamster cheek pouch. Bombesin increased, and RC-3095 decreased, phosphorylation in these samples. In the human hepatoma sample and surrounding tissue, these ligands altered the phosphorylation of the same substrates affected by EGF. EGF and bombesin stimulated phosphorylation synergistically in the hamster samples and the hepatoma. Bombesin-induced phosphorylation was greater in tissue surrounding the hepatoma, whereas RC-3095 was more effective in inhibiting phosphorylation in the hepatoma itself. This cancer, therefore, could be endogenously stimulated by gastrin-releasing peptide. These observations support the hypothesis that bombesin stimulates growth of tissues and tumors by amplifying the phosphorylation response to EGF. The growth inhibitory response to RC-3095, or other bombesin analogs, of individual tumors may be prognosed by in vitro phosphorylation assays using the samples from the patient's tumor.

IT **138147-78-1**, RC-3095
RL: BIOL (Biological study)
(protein phosphorylation in response to, in **neoplasm**)

L7 ANSWER 18 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:209063 HCAPLUS
DOCUMENT NUMBER: 120:209063
TITLE: Inhibitory effect of bombesin receptor antagonist RC-3095 on the growth of human pancreatic cancer cells in vivo and in vitro
AUTHOR(S): Qin, Yunfeng; Ertl, Tibor; Cai, Ren Zhi; Halmos, Gabor; Schally, Andrew V.
CORPORATE SOURCE: Endocr. Polypept. Cancer Inst., Veterans Aff. Med. Cent., New Orleans, LA, 70146, USA
SOURCE: Cancer Res. (1994), 54(4), 1035-41
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this study, the authors investigated the effect of bombesin/GRP antagonist RC-3095 on the growth of CFPAC-1 human pancreatic cancer cells transplanted to nude mice or cultured in vitro. Nude mice bearing xenografts of the CFPAC-1 cell line received s.c. injections of RC-3095 (10 .mu.g twice a day) or the vehicle (control) for 25 days. Chronic administration of RC-3095 inhibited the growth of CFPAC-1 tumors in nude mice as shown by a significant decrease in tumor vol. throughout the period of treatment. Tumor vol. doubling time was prolonged by RC-3095 treatment from 7.2 days to 10 days, and the tumor growth rate was decreased by 49%. In mice treated with RC-3095, the tumor growth delay time was 5.8 days. Treatment with RC-3095 decreased the final tumor wt. by 37% and reduced DNA and protein contents in tumor tissues by 44 and 39.9%, resp., compared to the controls. In cultures of the CFPAC-1 cell line, the addn. of bombesin (1-14) (1 pM-0.1 .mu.M) to the medium induced a dose-dependent increase in cell no. RC-3095 at 1 nM concn. effectively inhibited the bombesin-stimulated growth of CFPAC-1 cells in cultures. In the presence of 1 .mu.Ml RC-3095 in the culture medium, the bombesin-induced growth of CFPAC-1 cells was totally suppressed. Bombesin was also shown to stimulate the DNA synthesis in CFPAC-1 cells in vitro as based on [3H]thymidine incorporation assay. When the cells were cultured in the presence of 1-100 nM bombesin, the uptake of [3H]thymidine by the cells was increased by 89-131%. RC-3095 inhibited both the basal and bombesin-stimulated DNA synthesis of CFPAC-1 cells. Addn. of RC-3095 (10-100 nM) alone to the cultures caused a 39-40% decrease in the [3H]thymidine incorporation by the cells. Concomitant addn. of RC-3095 (1 .mu.M) and bombesin (1-100 nM) to the cultures induced a significant redn.

in the uptake of [3H]thymidine by the cells compared to the values obtained with bombesin alone. Receptor binding assays showed the presence of two classes of specific binding sites for bombesin on CFPAC-1 cells, one with high affinity (Kd = 4.25 NM) and low capacity (Bmax = 0.268 pmol/106 cells) and and the other with low affinity (Kd = 321.70 nM) and high capacity (Bmax = 3.991 pmol/106 cells). Antagonist RC-3095 inhibited the binding of 125I-Tyr4-bombesin to CFPAC-1 cell membranes in a dose-dependent manner. These observations suggest that bombesin acts as a growth factor and stimulates proliferation of CFPAC-1 human pancreatic cancer through specific receptors for bombesin/GRP present on the cells. RC-3095 appears to inhibit the growth of CFPAC-1 cells by blocking the interaction of bombesin with its receptors. The bombesin/GRP receptor antagonist RC-3095 could be considered for the development of new approaches for treatment of human pancreatic cancers.

IT **138147-78-1**, RC-3095
RL: BIOL (Biological study)
(pancreas **cancer** inhibition by, as bombesin receptor antagonist, in human cells in lab. animals)

L7 ANSWER 19 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:70217 HCAPLUS
DOCUMENT NUMBER: 120:70217
TITLE: Inhibitory effects of somatostatin analog RC-160 and bombesin/gastrin-releasing peptide antagonist RC-3095 on the growth of the androgen-independent Dunning R-3327-AT-1 rat prostate cancer
AUTHOR(S): Pinski, Jacek; Reile, Herta; Halmos, Gabor; Groot, Kate; Schally, Andrew V.
CORPORATE SOURCE: Endocr. Polypept. Cancer Inst., Veterans Aff. Med. Cent., New Orleans, LA, 70146, USA
SOURCE: Cancer Res. (1994), 54(1), 169-74
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of somatostatin analog RC-160 and bombesin/gastrin releasing-peptide (GRP) antagonist RC-3095 were evaluated in Copenhagen rats bearing the anaplastic, androgen-independent Dunning R3327-AT-1 prostate adenocarcinoma. In the first expt., RC-160 was given in the form of microcapsules releasing 60 .mu.g/day/rat. RC-3095 was administered from implanted Alzet osmotic minipumps liberating 100 .mu.g/day/rat. After 32 days, tumor vols. and wts. were significantly reduced by RC-160 as compared with the control group. Tumor doubling time in rats treated with RC-160 was significantly longer than in controls. Bombesin/GRP antagonist RC-3095 also significantly reduced tumor vol. after 7 days of treatment, but after 18 days the inhibition in tumor vol. was no longer significant. Tumor growth was not suppressed by castration. In the 2nd expt., 3-mm3 fragments of Dunning R-3327-AT-1 tumor were implanted orthotopically into the prostates of Copenhagen rats to evaluate the survival time of animals bearing this cancer during treatment with RC-160 released from Alzet osmotic minipumps at a dose of 100 .mu.g/day/rat. Treatment with RC-160 significantly prolonged the mean survival time of rats by 5.3 days as compared to control animals. In both experimentals, therapy with RC-160 significantly decreased serum growth hormone or insulin-like growth factor I levels. In the first expt., receptor assays on R-3327-AT-1 tumor membranes showed high affinity binding sites for somatostatin, bombesin, and epidermal growth factor. At the end of the treatment, receptors for epidermal growth factor were significantly down-regulated by treatment with RC-160 but not with RC-3095. The binding capacity of bombesin receptors was reduced to nondetectable levels after the treatment with RC-3095. In cell cultures, high affinity binding sites for bombesin/GRP were found on intact Dunning R-3327-AT-1 cells, but receptors for somatostatin could not be detected. Proliferation of the AT-1 cell line was significantly inhibited by antagonist RC-3095. However, no effect on tumor cell growth in vitro was obsd. with analog RC-160. The authors' results demonstrate that somatostatin analog RC-160 and bombesin/GRP antagonist RC-3095 can inhibit the growth of the

androgen-independent Dunning R-3327-AT-1 prostatic cancer in rats, although the remission produced by RC-3095 may be of short duration due to a down-regulation of bombesin receptors. The authors' work suggests the merit of further investigation as to whether these analogs can induce a possible delay in relapse and prolong survival in prostate cancer.

IT **138147-78-1**, RC-3095
RL: BIOL (Biological study)
(Dunning R-3327-AT-1 prostate **cancer** response to)

L7 ANSWER 20 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:617846 HCAPLUS
DOCUMENT NUMBER: 119:217846
TITLE: Somatostatin analog RC-160 and bombesin/gastrin-releasing peptide antagonist RC-3095 inhibit the growth of androgen-independent DU-145 human prostate cancer line in nude mice
AUTHOR(S): Pinski, Jacek; Halmos, Gabor; Schally, Andrew V.
CORPORATE SOURCE: Endocrine, Polypeptide Cancer Inst., Veterans Aff. Med. Cent., New Orleans, LA, 70146, USA
SOURCE: Cancer Lett. (Shannon, Irel.) (1993), 71(1-3), 189-96
CODEN: CALEDQ; ISSN: 0304-3835
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Nude mice bearing xenografts of the androgen-independent human prostate cancer DU-145 were treated for 4-5 wk with somatostatin analog RC-160 or the bombesin/gastrin-releasing peptide (GRP) antagonist RC-3095. Tumor growth in animals treated with somatostatin analog RC-160 at a dose of 100 .mu.g/day s.c. was inhibited within 14 days of the start of the expt. At necropsy, in mice given RC-160, tumor wt. and vol. were decreased compared with control mice. Treatment with RC-3095 at a dose of 20 .mu.g/day s.c. also suppressed tumor growth, the inhibition being significant after 2 wk, but the redn. in tumor and wt. was smaller than that produced by RC-160. Therapy with RC-160 decreased serum GH and gastrin levels. Specific binding sites for bombesin, somatostatin and EGF were found in the Du-145 tumor membranes. Receptors for EGF were down-regulated after therapy with RC-3095 and RC-160. The finding that somatostatin analog RC-160 and bombesin/GRP antagonist RC-3095 inhibit the growth of androgen-independent prostate tumor in mice might be of practical importance for human prostate cancer therapy.

IT **138147-78-1**, RC-3095
RL: BIOL (Biological study)
(prostate **cancer** cell growth from human inhibition by, in mouse)

L7 ANSWER 21 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:552487 HCAPLUS
DOCUMENT NUMBER: 119:152487
TITLE: Effect of bombesin, gastrin-releasing peptide (GRP)(14-27) and bombesin/GRP receptor antagonist RC-3095 on growth of nitrosamine-induced pancreatic cancers in hamsters
AUTHOR(S): Szepeshazi, Karoly; Schally, Andrew V.; Groot, Kate; Halmos, Gabor
CORPORATE SOURCE: Endocrine, Polypeptide CAncer Inst., Veterans Affairs Med. Cent., New Orleans, LA, 70146, USA
SOURCE: Int. J. Cancer (1993), 54(2), 282-9
CODEN: IJCNAW; ISSN: 0020-7136
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Female Syrian golden hamsters with N-nitroso-bis(2-oxopropyl)amine (BOP)-induced pancreatic cancers were treated for 2 mo with bombesin/gastrin-releasing peptide (GRP) antagonist D-Tpi6, Leu13.psi.(CH2NH)Leu14 bombesin(6-14) (RC-3095). Bombesin and GRP(14-27) were also administered alone and in combination with the antagonist RC-3095. RC-3095 exerted a dose-dependent inhibitory effect on growth of pancreatic cancers. The no. of animals with pancreatic cancers was

significantly lower in the group treated with 60 .mu.g/day of RC-3095 and the wt. of tumorous pancreata was reduced. Administration of bombesin or GRP alone did not stimulate the growth of pancreatic tumors and, in fact, had a slightly suppressive effect on cancers. Bombesin and GRP(14-27) given together with RC-3095 did not nullify the inhibitory effect of the antagonist on pancreatic cancer growth. Actually, a greater inhibition of pancreatic tumors was obsd. after administration of RC-3095 together with bombesin or GRP, than with RC-3095 alone. The mechanism of action of bombesin, GRP, and bombesin antagonists on pancreatic cancers appears to be complex. The inhibitory effect of bombesin antagonists on pancreatic cancer growth was accompanied by a decrease in the binding capacity of EGF receptors in tumor membranes. Administration of bombesin also caused a down-regulation of EGF receptors, and the greatest decrease in binding capacity of EGF receptors was obsd. after treatment with RC-3095 in combination with GRP. Inhibition of pancreatic cancer can thus be tentatively explained by some common pathways in the action of bombesin, GRP and their antagonists, and these could be mediated by interference with EGF-receptor mechanisms.

IT **138147-78-1**, RC-3095
RL: BIOL (Biological study)
(**neoplasm**-inhibitory activity of, mechanism of)

L7 ANSWER 22 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:183952 HCAPLUS
DOCUMENT NUMBER: 118:183952
TITLE: Peptide analogs alter the progression of premalignant lesions, as measured by Photofrin fluorescence
AUTHOR(S): Liebow, Charles; Crean, David H.; Schally, Andrew V.; Mang, Thomas S.
CORPORATE SOURCE: Photodyn. Therapy Cent., Roswell Park Cancer Inst., Buffalo, NY, 14263, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1993), 90(5), 1897-901
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The somatostatin analog RC-160 and the bombesin/gastrin-releasing peptide antagonist RC-3095 were infused at 2 .mu.g/day via miniosmotic pumps implanted s.c. in hamsters with premalignant disease to examine the effect of these peptides on cancer promotion and progression. These analogs have been shown to inhibit growth of certain tumors, esp. those that overexpress tyrosine kinase activity. Progression of premalignant lesions initiated by applying 0.5% DMBA to the hamster buccal cheek pouch was measured by Photofrin-induced fluorescence 24 h after injecting the porphyrin (1.0 mg/kg) by using in vivo fluorescence photometry. This method of monitoring progression was reaffirmed by the observations that fluorescence increased as compared with controls in lesions receiving 4 addnl. weeks of continuous promotion by DMBA application and in lesions receiving transient promotion by laser incision. Twelve weeks after treatment, fluorescence had decreased among animals treated for 2 wk with RC-3095 (control, 0.53 vs. RC-3095, 0.28 vs. RC-160, 0.24). These data were obtained 20 wk after DMBA initiation. Thus, treatment with RC-160 and RC-3095 decreased the progression, measured by fluorescence, compared with control animals. In addn., there was also an abs. continuous decrease in fluorescence for the 22 wk after the cessation of RC-160 treatment. That the changes in tumor progression produced by RC-160 extended beyond the treatment period supports the hypothesis that the changes were irreversible. Histopathol. anal. revealed normal tissue and/or mild-moderate dysplasia in hamster buccal mucosa treated with the RC-160 (an improvement compared to pretreatment), whereas 40% of the animals receiving no treatment after DMBA initiation developed invasive squamous cell carcinomas after 20 wk. Evidently the antagonists of bombesin/gastrin-releasing peptide can delay the development of malignancies and the agonists of somatostatin can potentially reverse this development.

IT **138147-78-1**, RC-3095

RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**neoplasm** inhibition by)

L7 ANSWER 23 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:116348 HCAPLUS
DOCUMENT NUMBER: 118:116348
TITLE: Growth inhibition of estrogen-dependent and estrogen-independent MXT mammary cancers in mice by the bombesin and gastrin-releasing peptide antagonist RC-3095
AUTHOR(S): Szepeshazi, Karoly; Schally, Andrew V.; Halmos, Gabor; Groot, Kate; Radulovic, Sinisa
CORPORATE SOURCE: Endocr. Polypept. Cancer Inst., Veterans Aff. Med. Cent., New Orleans, LA, 70146, USA
SOURCE: J. Natl. Cancer Inst. (1992), 84(24), 1915-22
CODEN: JNCIEQ; ISSN: 0027-8874
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Antagonists of bombesin and gastrin-releasing peptide, including RC-3095, inhibit the growth of pancreatic, colonic, and prostatic cancers in exptl. animals. This effect is assocd. with a substantial decrease in EGF receptor levels in pancreatic and colon cancers. The effects of the synthetic bombesin and gastrin-releasing peptide receptor antagonist [D-Tpi6,Leu13.psi.(CH2NH)-Leu14]bombesin(6-14) (RC-3095) on the growth of hormone-dependent and hormone-independent MXT mouse mammary cancers were studied in vivo. Female mice bearing the MXT carcinomas were treated with small doses (20 .mu.g/day) of RC-3095 administered from osmotic minipumps. Groups of mice with estrogen-independent tumors received RC-3095, bombesin, or gastrin-releasing peptide(14-27) at 20 .mu.g/day. Tumor vol. and wt., mitotic index, apoptosis (programmed cell death), and argyrophilic nucleolar organizer regions were detd. as indicators of tumor cell proliferation. The levels of EGF receptors and bombesin were measured in tumor membrane fractions. The growth of both estrogen-dependent and estrogen-independent MXT cancers was inhibited by RC-3095. Bombesin or gastrin-releasing peptide had no effect on the growth of estrogen-independent tumors. In estrogen-independent cancers, the tumor inhibition was assocd. with a decrease in the capacity of EGF receptors from 0.21 to 0.03 pmol/mg membrane protein in control and RC-3095-treated groups, resp. Bombesin antagonists should be considered for breast cancer therapy.
IT **138147-78-1**, RC-3095
RL: PRP (Properties)
(**antitumor** effects of, in breast **cancer**, estrogen dependence in relation to)

L7 ANSWER 24 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1992:525018 HCAPLUS
DOCUMENT NUMBER: 117:125018
TITLE: Inhibition of growth of PC-82 human prostate cancer line xenografts in nude mice by bombesin antagonist RC-3095 or combination of agonist [D-Trp6]-luteinizing hormone-releasing hormone and somatostatin analog RC-160
AUTHOR(S): Milovanovic, Slobodan R.; Radulovic, Sinisa; Groot, Kate; Schally, Andrew V.
CORPORATE SOURCE: Endocr. Polypept. Cancer Inst., Veterans Adm. Med. Cent., New Orleans, LA, 70146, USA
SOURCE: Prostate (N. Y.) (1992), 20(4), 269-80
CODEN: PRSTDS; ISSN: 0270-4137
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The antitumor activity of bombesin antagonist RC-3095 and the combination of [D-Trp6]LH-RH and somatostatin analog RC-160 in human prostate cancer line xenografts in nude mice was investigated. The efficacy of the LH-RH and somatostatin analogs combination was greater than the therapeutic

effect of either analog alone. Addnl., results suggested that bombesin antagonists may be useful in the management of prostate carcinoma.

IT **138147-78-1**, RC 3095
RL: BIOL (Biological study)
(prostate **cancer** inhibition by, from human)

L7 ANSWER 25 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1992:483811 HCAPLUS
DOCUMENT NUMBER: 117:83811
TITLE: The binding of bombesin and somatostatin and their analogs to human colon cancers
AUTHOR(S): Radulovic, Sinisa S.; Milovanovic, Slobodan R.; Cai, Ren Zhi; Schally, Andrew V.
CORPORATE SOURCE: Cancer Inst., VA Med. Cent., New Orleans, LA, 70146, USA
SOURCE: Proc. Soc. Exp. Biol. Med. (1992), 200(3), 394-401
CODEN: PSEBAA; ISSN: 0037-9727
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Specific receptors for bombesin/gastrin-releasing peptide, somatostatin, and EGF were investigated in 15 human colon cancer specimens. Eight of 15 clin. specimens (15%) of colon cancer showed the presence of somatostatin receptors. Octapeptide somatostatin analogs, RC 160 and RC 121, showed 10 times higher binding affinity for somatostatin receptors on colon cancer membranes than did somatostatin. Anal. of 125I-Tyr4-bombesin binding data revealed the presence of specific binding sites in 6 (40%) specimens of human colon cancer. Scatchard anal. of 125I-labeled bombesin indicated a single class of receptors in 3 specimens with an apparent Kd value of 2.5 nM and 2 classes of receptors with high (Kd = 0.4 nM) and low affinity (Kd = 1.6 .mu.M) in 3 other specimens. The 125I-Tyr4-bombesin binding capacities in the colon cancers for high affinity binding sites were from 6 to 228 fmol/mg protein and for low affinity binding sites 76 pmol/mg protein. None of the membrane prepns. made from normal colonic mucosa specimens showed specific binding for 125I-Tyr4-bombesin. Five pseudononapeptide (.psi.13-14)bombesin-(6-14) antagonists, with different modifications at positions 6 and 14, synthesized in our lab., inhibited the binding of 125I-Tyr4-bombesin in nanomolar concns. No correlation was found between the degree of differentiation and the presence of binding sites for somatostatin or bombesin. Specific binding of EGF was detected in 80% of colon cancer specimens. EGF binding capacity in colon cancer membranes was on av. twice as high as in normal colon mucosa (50 vs. 28 fmol/mg protein, resp.). Specific binding sites for somatostatin and EGF, but not bombesin, were also demonstrated in human colon cancer cell line HT-29. In HCT-116 colon cancer line only EGF receptors were found. These receptor findings and in vivo studies on inhibition of colon cancer growth support the merit of continued evaluation of somatostatin analogs and bombesin/gastrin-releasing peptide antagonists in the management of colonic carcinoma.

IT **138147-78-1**, RC 3095
RL: PROC (Process)
(receptor binding of, in human colon **cancer**)

L7 ANSWER 26 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1992:15459 HCAPLUS
DOCUMENT NUMBER: 116:15459
TITLE: Inhibition of growth of HT-29 human colon cancer xenografts in nude mice by treatment with bombesin/gastrin releasing peptide antagonist (RC-3095)
AUTHOR(S): Radulovic, Sinisa; Miller, Glenn; Schally, Andrew V.
CORPORATE SOURCE: Endocr., Polypept., Cancer Inst., Veterans Aff. Med. Cent., New Orleans, LA, 70146, USA
SOURCE: Cancer Res. (1991), 51(21), 6006-9
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Nude mice bearing xenografts of HT-29 human colon cancer cell line were treated for 4 wk with a [D-Trp6] agonist of LH-releasing hormone (LH-RH), somatostatin analog RC-160, and bombesin/gastrin releasing peptide antagonist RC-3095. Slight inhibitory effect of [D-Trp6]-LH-RH microcapsules releasing 25 .mu.g/day on tumor growth was obsd. that could be due to sex steroid deprivation. Microcapsules of RC-160, releasing 50 .mu.g/day, reduced tumor vol. after 21 and 24 days of treatment. RC-3095 at 20 .mu.g/day administered by daily s.c. injections or by continuous infusion using Alzet osmotic minipumps, had the greatest inhibitory effect on tumor growth. Tumor vol., percentage change in tumor vol., and tumor wts. were decreased.

IT **138147-78-1**, RC 3095
RL: PRP (Properties)
(**antitumor** effects of, in colon)

L7 ANSWER 27 OF 27 HCAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1992:15458 HCAPLUS
DOCUMENT NUMBER: 116:15458
TITLE: Inhibitory effect of bombesin/gastrin-releasing peptide antagonist RC-3095 and high dose of somatostatin analogue RC-160 on nitrosamine-induced pancreatic cancers in hamsters
AUTHOR(S): Szepeshazi, Karoly; Schally, Andrew V.; Cai, Ren Zhi; Radulovic, Sinisa; Milovanovic, Slobodan; Szoke, Balasz
CORPORATE SOURCE: Med. Sch., Tulane Univ., New Orleans, LA, 70112, USA
SOURCE: Cancer Res. (1991), 51(21), 5980-6
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
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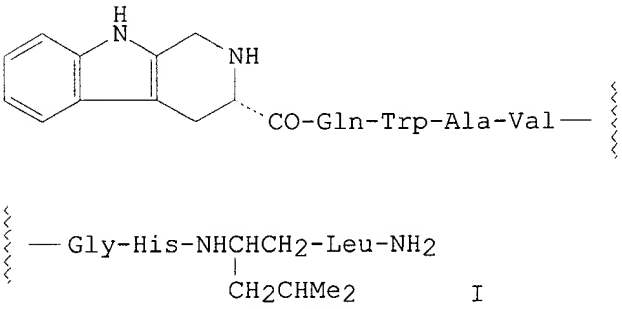

I

AB Female Syrian golden hamsters with N-nitrosobis(2-oxopropyl)amine-induced pancreatic cancers were treated for 2 mo with the bombesin receptor antagonist RC-3095 (I) administered s.c. with osmotic minipumps releasing 20 .mu.g/day of the agent. The results were compared to those obtained by treatment with the somatostatin analog RC-160 (35 and 150 .mu.g/day), [D-Trp6]LH-releasing hormone (25 .mu.g/day), and the acetylated somatostatin analog RC-160-II (30 .mu.g/day). All peptide analogs showed tumor inhibition by at least one of the measured parameters. RC-3095 and the high dose of RC-160 had the greatest inhibitory effect on pancreatic cancers. A decrease in the no. of animals with tumors, reduced pancreatic wt., 87-89% inhibition of tumorous pancreas wt., and a diminution in the no. of tumor nodules and argyrophilic nucleolar organizer region count in tumor cell nuclei were obsd. Receptors for bombesin were detected in membranes of N-nitrosobis(2-oxopropyl)amine-induced pancreatic tumors and these receptors were not down-regulated after treatment with the bombesin antagonist. In hamsters treated with bombesin antagonists, tumor inhibition might be explained by a decrease in the binding capacity of epidermal growth factor receptors in pancreatic cancers. RC-160-II had a similar inhibitory effect on the tumors as RC-160. The increase in the

dose of RC-160 improved the therapeutic response. This finding should be taken into account in clin. use of this somatostatin analog. RC-3095 might be considered as a possible agent for the therapy of human exocrine pancreatic cancer.

IT **138147-78-1**
RL: PRP (Properties)
(**antitumor** effects of, in pancreas **cancer**)

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L8 ANSWER 1 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **166774-43-2** REGISTRY
CN 1-7-Litorin (peptide), 1-[(3R)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid]-7-[N-[(1S)-1-[[(4R)-4-carboxy-3-thiazolidinyl]methyl]-3-methylbutyl]-L-histidinamide]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-7-Litorin (peptide), N2-[(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-3-yl)carbonyl]-7-[N-[1-[(4-carboxy-3-thiazolidinyl)methyl]-3-methylbutyl]-L-histidinamide]-, [2(R),7[R-(R*,S*)]]-
OTHER NAMES:
CN RC 3910-II
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LC STN Files: CA, CAPLUS, TOXLIT

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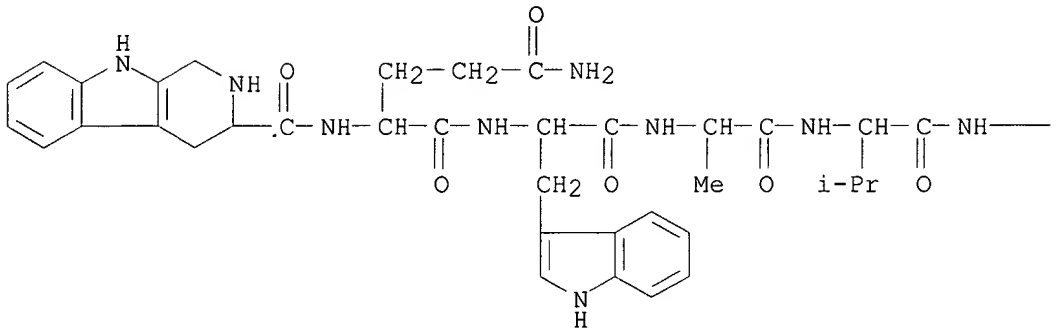
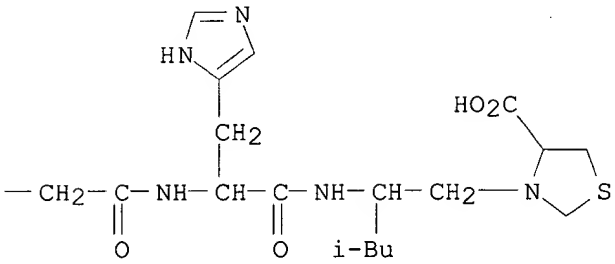


PAGE 1-B



3 REFERENCES IN FILE CA (1967 TO DATE)
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REFERENCE 2: 124:194457

REFERENCE 3: 123:131996

L8 ANSWER 2 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **163878-62-4** REGISTRY
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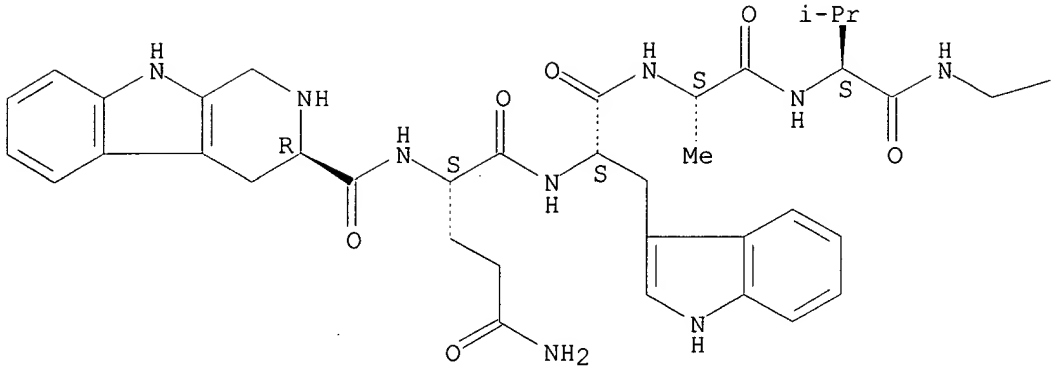
Absolute stereochemistry.

PAGE 1-A



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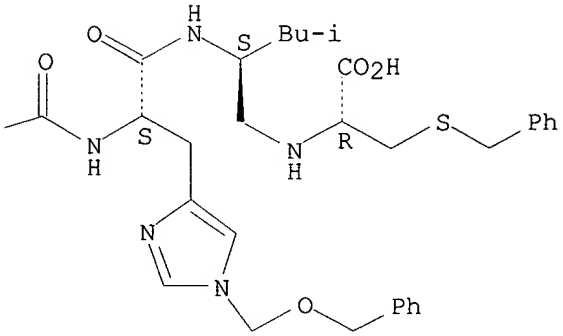

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1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 123:9930

L8 ANSWER 3 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **163878-60-2** REGISTRY
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FS PROTEIN SEQUENCE; STEREOSEARCH
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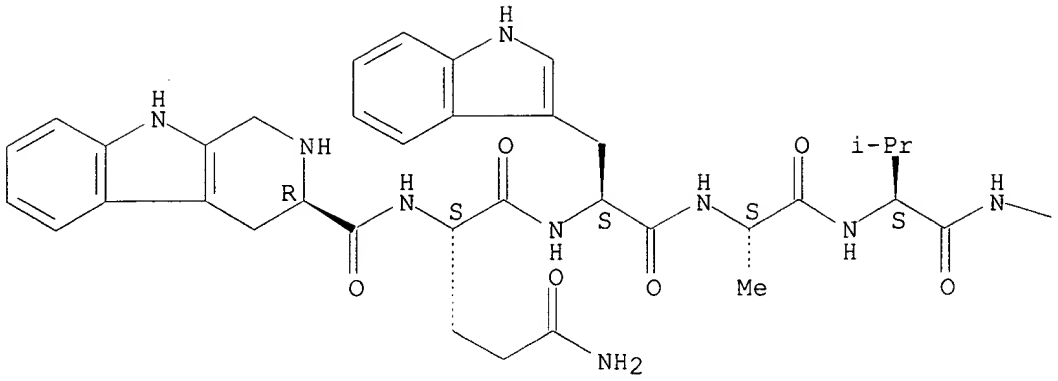
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

PAGE 1-A



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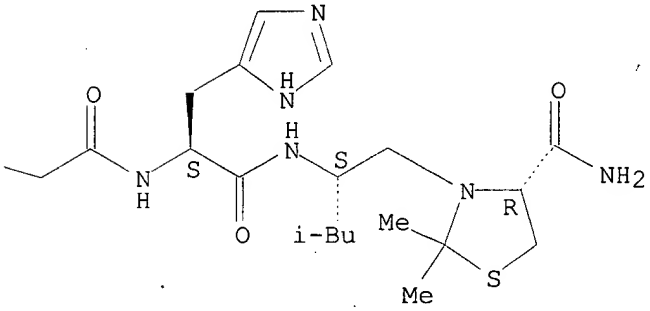


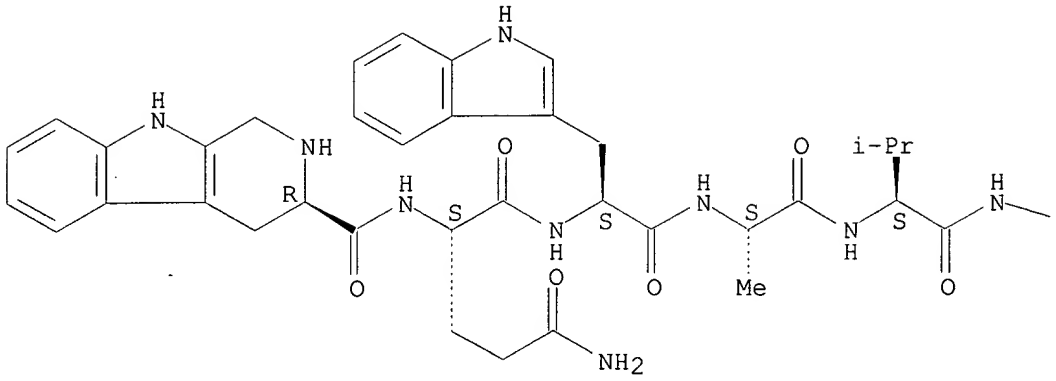
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 123:9930

L8 ANSWER 4 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **163878-59-9** REGISTRY
CN 4-9-Ranatensin, N2-[(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-3-yl)carbonyl]-9-[N-[1-[[4-(aminocarbonyl)-3-thiazolidinyl]methyl]-3-methylbutyl]-L-histidinamide]-, [4(R),9[R-(R*,S*)]]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C54 H73 N15 O9 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

PAGE 1-A



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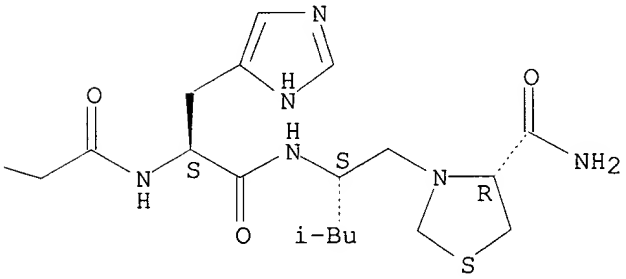

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 123:112728

REFERENCE 2: 123:9930

L8 ANSWER 5 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **163759-38-4** REGISTRY
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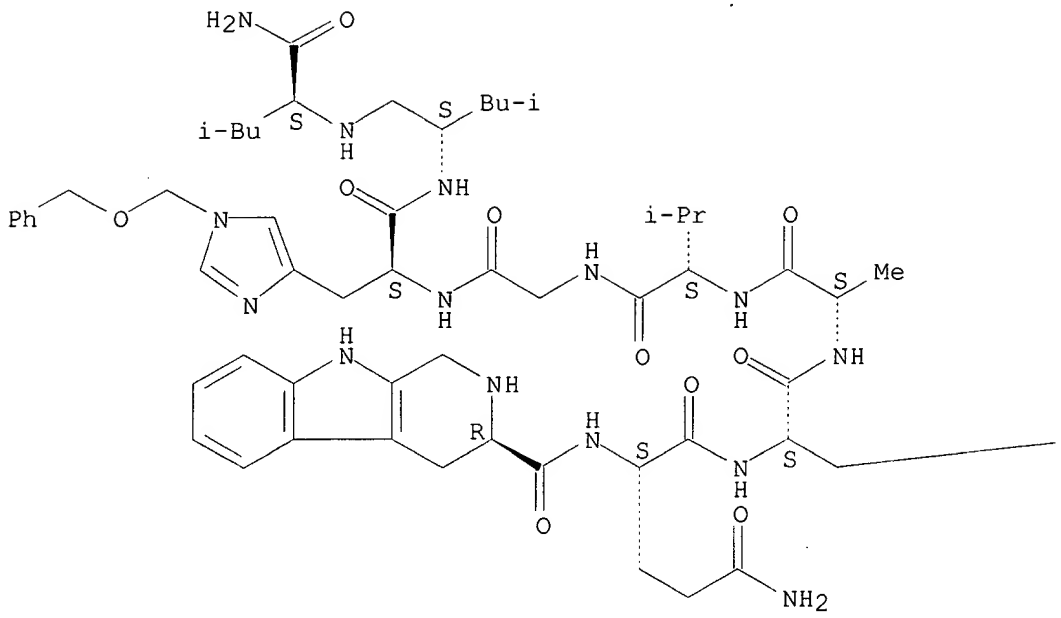
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C64 H87 N15 O10
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

PAGE 1-A



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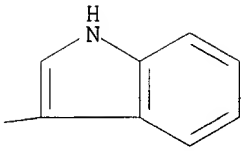

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 123:9930

L8 ANSWER 6 OF 12 REGISTRY COPYRIGHT 2000 ACS
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FS PROTEIN SEQUENCE; STEREOSEARCH
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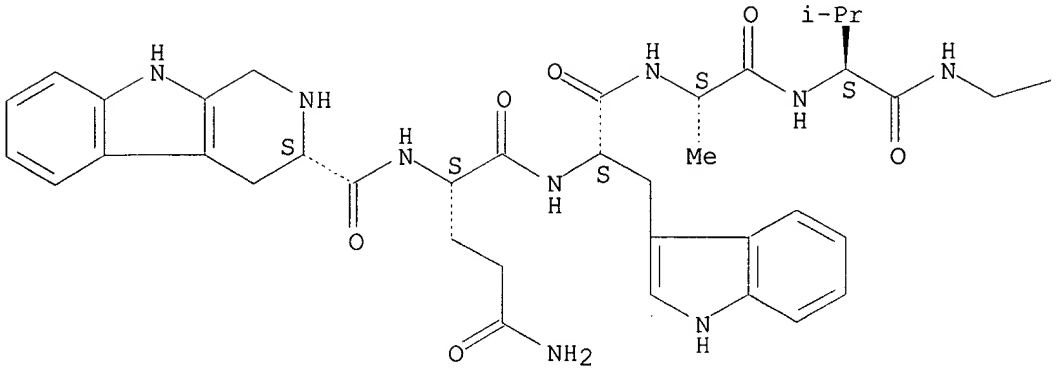
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

PAGE 1-A



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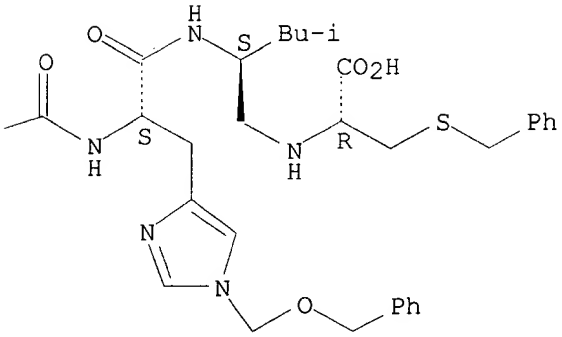

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1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 123:9930

L8 ANSWER 7 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **163759-34-0** REGISTRY
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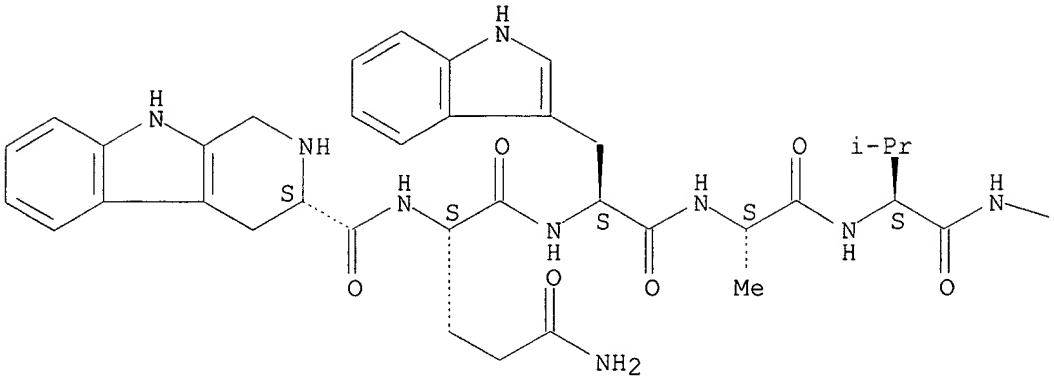
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C56 H77 N15 O9 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

PAGE 1-A



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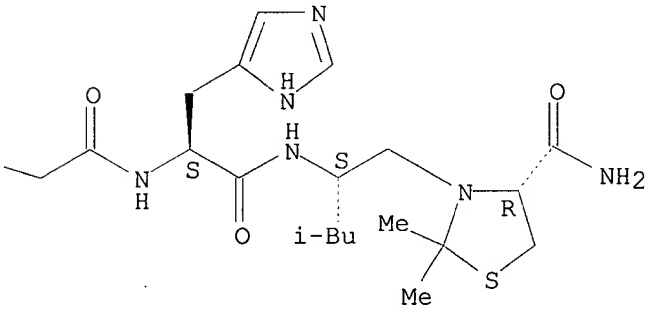

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 123:9930

L8 ANSWER 8 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **163759-26-0** REGISTRY
CN 4-9-Ranatensin, N2-[(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-3-yl)carbonyl]-9-[N-[1-[[4-(aminocarbonyl)-3-thiazolidinyl]methyl]-3-methylbutyl]-L-histidinamide]-, [4(S),9[R-(R*,S*)]]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
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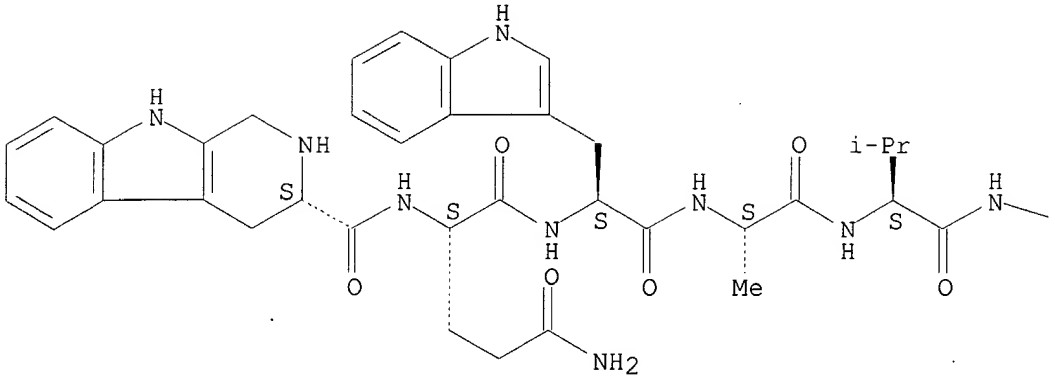
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

PAGE 1-A



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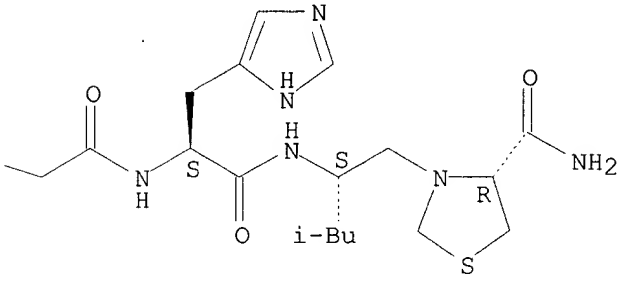


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 123:112728

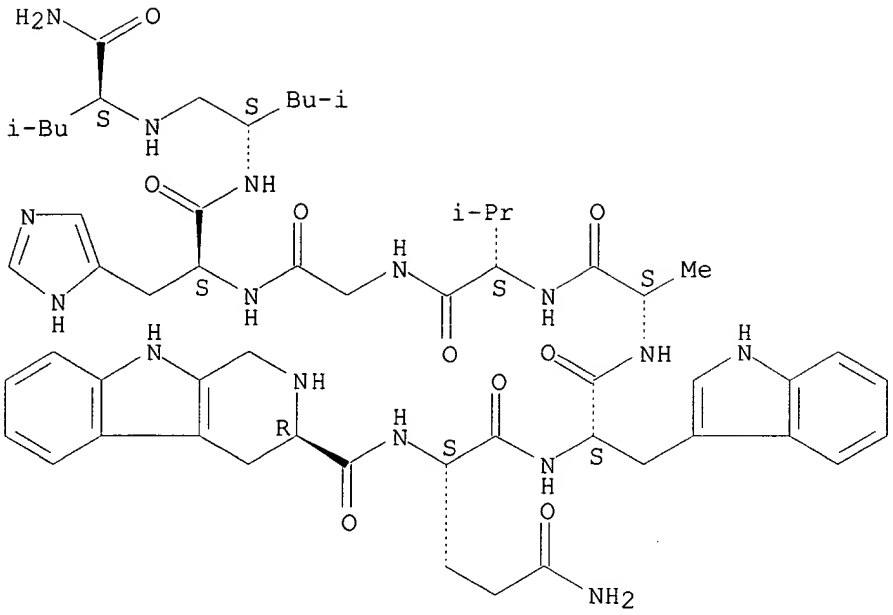
REFERENCE 2: 123:9930

L8 ANSWER 9 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **162666-31-1** REGISTRY
CN L-Histidinamide, N2-[(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-3-yl)carbonyl]-L-glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-N-[1-[[[1-(aminocarbonyl)-3-methylbutyl]amino]methyl]-3-methylbutyl]-, [1(R),6[S-(R*,R*)]]-, monoacetate (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrido[3,4-b]indole, L-histidinamide deriv. (9CI)
OTHER NAMES:
CN D 22213
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C56 H79 N15 O9 . C2 H4 O2
SR CA
LC STN Files: CA, CAPLUS, DRUGNL, DRUGUPDATES, TOXLIT

CM 1

CRN 138147-78-1
CMF C56 H79 N15 O9

Absolute stereochemistry.



CM 2

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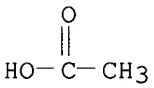
CMF C2 H4 O2



1 REFERENCES IN FILE CA (1967 TO DATE)
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REFERENCE 1: 122:255644

L8 ANSWER 10 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **143491-06-9** REGISTRY
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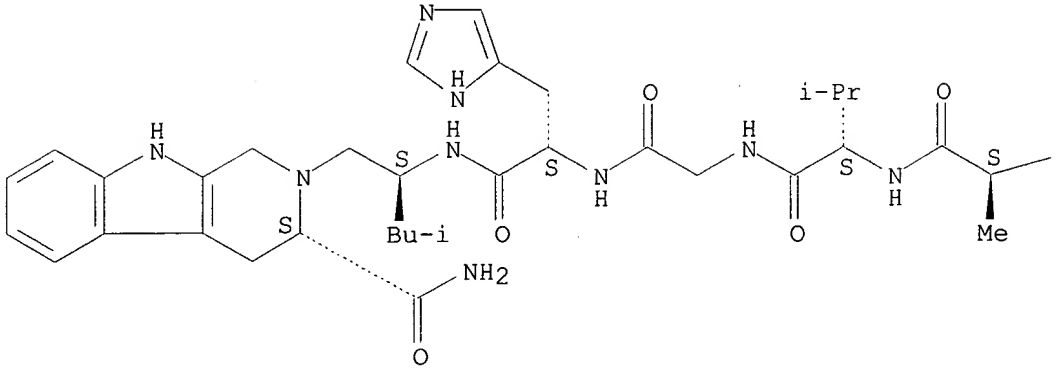
OTHER CA INDEX NAMES:
CN 1H-Pyrido[3,4-b]indole, L-histidinamide deriv.
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C62 H78 N16 O9
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

PAGE 1-A



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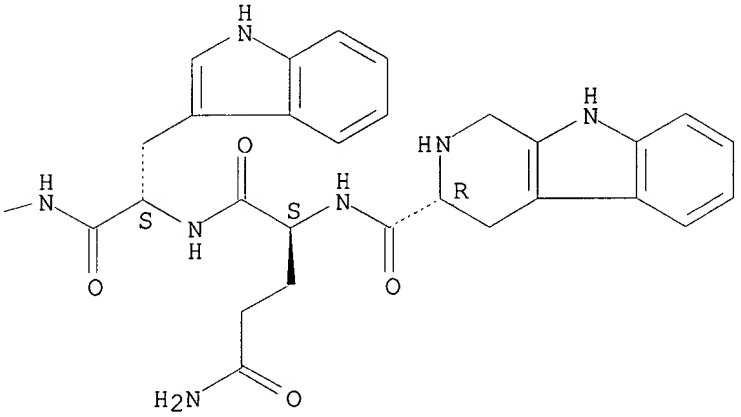

2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 123:9930

REFERENCE 2: 117:192350

L8 ANSWER 11 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **142824-94-0** REGISTRY
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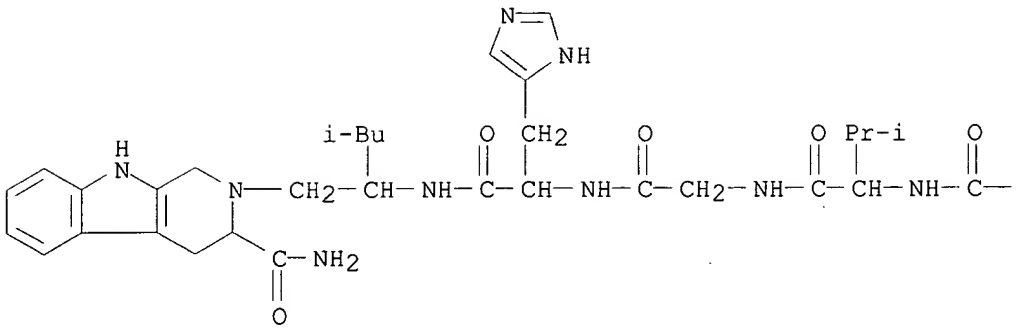
OTHER CA INDEX NAMES:
CN 1H-Pyrido[3,4-b]indole, L-histidinamide deriv.
OTHER NAMES:
CN RC 3440
FS PROTEIN SEQUENCE
MF C62 H78 N16 O9
SR CA
LC STN Files: ADISINSIGHT, CA, CANCERLIT, CAPLUS, MEDLINE, TOXLIT, USPATFULL

PAGE 1-A



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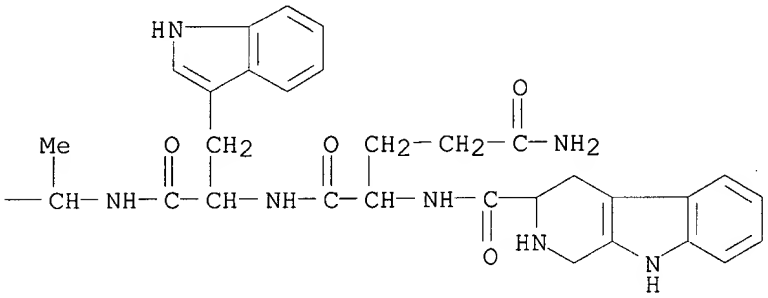

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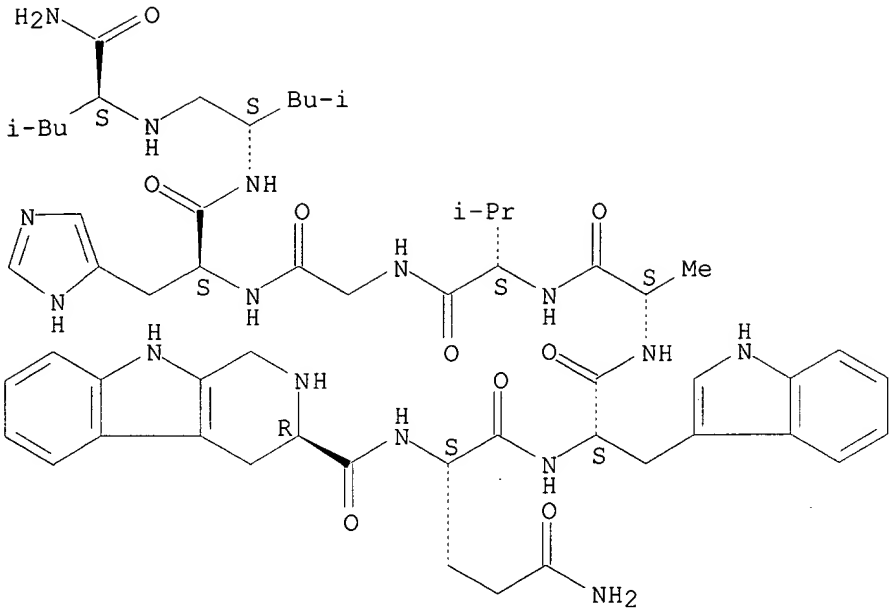
REFERENCE 2: 117:192350

REFERENCE 3: 117:83567

L8 ANSWER 12 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **138147-78-1** REGISTRY
CN L-Leucinamide, (3R)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carbonyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-L-histidyl-L-leucyl-.psi.(CH2-NH)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrido[3,4-b]indole, L-histidinamide deriv.
CN L-Histidinamide, N2-[(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-3-yl)carbonyl]-L-glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-N-[1-[[[1-(aminocarbonyl)-3-methylbutyl]amino]methyl]-3-methylbutyl]-, [1(R),6[S-(R*,R*)]]-
OTHER NAMES:
CN RC 3095
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C56 H79 N15 O9
CI COM
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, CA, CANCERLIT, CAPLUS, CIN, DRUGNL, DRUGUPDATES, EMBASE, MEDLINE, PROMT, TOXLINE, TOXLIT, USPATFULL

Absolute stereochemistry.



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REFERENCE 2: 130:60697

REFERENCE 3: 129:144603

REFERENCE 4: 127:314475

REFERENCE 5: 126:246412

REFERENCE 6: 125:237839

REFERENCE 7: 124:283275

REFERENCE 8: 124:194457

REFERENCE 9: 124:105565

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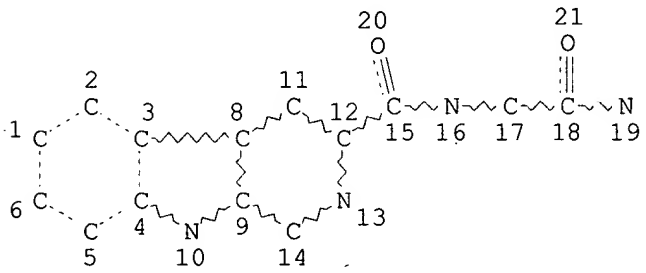


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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  20

STEREO ATTRIBUTES: NONE
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L7   ANSWER 1 OF 27  HCAPLUS  COPYRIGHT 2000 ACS
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ACCESSION NUMBER: 1999:559428 HCAPLUS
DOCUMENT NUMBER: 131:194602
TITLE: Growth inhibition of experimental pancreatic cancers and sustained reduction in epidermal growth factor receptors during therapy with hormonal peptide analogs
AUTHOR(S): Szepeshazi, Karoly; Halmos, Gabor; Schally, Andrew V.; Arencibia, Jose M.; Groot, Kate; Vadillo-Buenfil, Manuel; Rodriguez-Martin, Eulalia
CORPORATE SOURCE: Endocrine, Polypeptide Cancer Inst., VA Med. Center, New Orleans, LA, 70112, USA
SOURCE: J. Cancer Res. Clin. Oncol. (1999), 125(8/9), 444-452
CODEN: JCROD7; ISSN: 0171-5216
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In view of tumor growth inhibition epidermal growth factor (EGF) receptor redn. was studied in cancers. Hamsters with nitrosamine-induced pancreatic cancers were treated for 8 wk with bombesin/gastrin-releasing peptide (GRP) antagonist RC-3095, somatostatin analog RC-160, or the LH-releasing hormone antagonist cetrorelix by sustained delivery systems releasing 20, 35, and 20 .mu.g/day, resp. RC-3095 or cetrorelix resulted in an early (day 10) and sustained redn. (71% or 69%, resp.) on pancreatic tumors. RC-160 showed a 60% decrease only after 20 days. Histol. the decrease in argyrophilic nucleolar organizer regions showed a correlation with receptor redn. The concn. returned to control level 4 days after RC-3095 cessation. RC-160 single injection decreased receptors on pancreatic cancers by 31% 3 h after administration, returning to normal at 6 h. RC-3095 and cetrorelix single injections caused a 67% and 59% decline, resp., only 6 h after injection and the concn. remained low for 24 h.

IT **138147-78-1**, RC-3095
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(growth inhibition of pancreatic **cancers** and sustained redn. in EGF receptors during hormonal peptide analog therapy)

L7 ANSWER 2 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:377735 HCAPLUS
DOCUMENT NUMBER: 129:144603
TITLE: Inhibition of growth of MDA-MB-231 human breast cancer xenografts in nude mice by bombesin/gastrin-releasing peptide (GRP) antagonists RC-3940-II and RC-3095
AUTHOR(S): Miyazaki, M.; Lamharzi, N.; Schally, A. V.; Halmos, G.; Szepeshazi, K.; Groot, K.; Cai, R. Z.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans' Affairs Medical Center, Tulane University School of Medicine, New Orleans, LA, 70146, USA
SOURCE: Eur. J. Cancer (1998), 34(5), 710-717
CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bombesin or gastrin-releasing peptide (GRP) may act as autocrine growth factors and play a role in the initiation and progression of breast cancer. We investigated the effect of bombesin/GRP antagonists RC-3095 and RC-3940-II on the growth of the MDA-MB-231 estrogen-independent human breast cancer cell line xenografted into female nude mice. Bombesin/GRP antagonists, RC-3095 and RC-3940-II, were administered s.c. twice daily at a dose of 10 .mu.g for 5 wk. The growth of MDA-MB-231 tumors was inhibited during the treatment, as shown by a redn. in tumor vol. RC-3940-II and RC-3095 significantly decreased the final tumor vol. by 72.4% and 57.7%, resp., and greatly reduced tumor wts. RC-3940-II also significantly increased tumor doubling time and appeared to be more effective than RC-3095 in inhibiting the growth of MDA-MB-231 breast cancers. Serum gastrin and insulin-like growth factor-I (IGF-I) levels in animals treated with RC-3095 or RC-3940-II showed no significant changes

as compared with controls. There was a significant decrease in the no. of binding sites for epidermal growth factor (EGF), as well as bombesin, in tumor cells after chronic treatment with RC-3095 or RC-3940-II, which might be related to inhibition of tumor growth. Reverse transcription polymerase chain reaction, followed by Southern blot anal., also showed a redn. in the expression of mRNA for EGF receptors in the group treated with RC-3940-II. Our findings suggest that bombesin/GRP antagonists such as RC-3095 or RC-3940-II could be considered for endocrine therapy for estrogen-independent breast cancers, but further investigations are necessary.

IT **138147-78-1**, RC-3095
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of human breast **cancer** xenografts in nude mice by bombesin/gastrin-releasing peptide (GRP) antagonists RC-3940-II and RC-3095)

L7 ANSWER 3 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:634427 HCAPLUS
DOCUMENT NUMBER: 127:314475
TITLE: A single in vivo administration of bombesin antagonist RC-3095 reduces the levels and mRNA expression of epidermal growth factor receptors in MXT mouse mammary cancers
AUTHOR(S): Szepeshazi, Karoly; Schally, Andrew V.; Halmos, Gabor; Lamharzi, Najib; Groot, Kate; Horvath, Judit E.
CORPORATE SOURCE: Veterans Affairs Medical Center, Endocrine, Polypeptide Cancer Institute, Tulane University School Medicine, New Orleans, LA, 70146, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1997), 94(20), 10913-10918
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Epidermal growth factor (EGF) and its receptors (EGFR) play important roles in tumorigenesis. In various exptl. cancers, treatment with antagonists of bombesin/gastrin-releasing peptide (BN/GRP) produces a redn. in EGFRs, concomitant to inhibition of tumor growth. To investigate the mechanisms involved, we monitored concns. of BN/GRP antagonist RC-3095 in serum of mice, rats, and hamsters given a single s.c. or i.v. injection of this analog. In parallel studies, we measured levels and mRNA expression of EGFRs in estrogen-dependent and independent MXT mouse mammary cancers, following a single s.c. administration of RC-3095 to tumor-bearing mice. Peak values of RC-3095 in serum was detected 2 min after i.v. or 15 min after s.c. injection. The levels of RC-3095 declined rapidly and became undetectable after 3-5 h. In the estrogen-dependent MXT tumors, the concn. of EGF receptors was reduced by about 60% 6 h following injection and returned to original level after 24 h. Levels of mRNA for EGFR fell parallel with the receptor no. and were nearly normal after 24 h. In the hormone-independent MXT cancers, the no. of EGFRs decreased progressively, becoming undetectable 6 h after injection of RC-3095, and returned to normal values at 24 h, but EGFR mRNA levels remained lower for 48 h. Thus, in spite of rapid elimination from serum, BN/GRP antagonist RC-3095 can induce a prolonged decrease in levels and mRNA expression of EGFRs. These findings may explain how single daily injections of BN/GRP antagonists can maintain tumor growth inhibition.

IT **138147-78-1**, RC-3095
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(a single in vivo administration of bombesin antagonist RC-3095 reduces the levels and mRNA expression of epidermal growth factor receptors in MXT mouse mammary **cancers**)

L7 ANSWER 4 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:107924 HCAPLUS

DOCUMENT NUMBER: 126:246412
TITLE: Reduction in receptors for bombesin and epidermal growth factor in xenografts of human small-cell lung cancer after treatment with bombesin antagonist RC-3095
AUTHOR(S): Halmos, Gabor; Schally, Andrew V.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, New Orleans, LA, 70146, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1997), 94(3), 956-960
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Antagonists of bombesin/gastrin-releasing peptide (BN/GRP) have been developed to inhibit the stimulatory effects of BN/GRP on the mitogenesis of tumor cells such as human small-cell lung carcinoma (SCLC). The mode of action of these antagonists is not completely understood. In this study, the authors evaluated the effect of BN/GRP antagonist RC-3095 on receptors for BN/GRP and epidermal growth factor (EGF) in H-128 human SCLC line xenografted into nude mice. Treatment with RC-3095, administered s.c. at a dose of 20 .mu.g/day per animal for 4 wk caused a 70% redn. in tumor vol. and wt. Membrane receptors for BN/GRP and EGF were characterized in untreated and treated animals. In the control group, [125I-Tyr4]BN was bound to a single class of specific, high affinity binding sites with a dissocn. const. (Kd) = 6.55 nM and maximal binding capacity (Bmax) = 512.8 fmol/mg membrane protein. Therapy with RC-3095 decreased the concn. of BN/GRP receptors on H-128 SCLC tumor membranes. Specific, high affinity binding sites for EGF with Kd = 1.78 nM and Bmax = 216.8 fmol/mg membrane protein were also found on the untreated H-128 SCLC tumors. Treatment with RC-3095 significantly decreased Bmax of receptors for EGF. The results indicate that the suppression of growth of H-128 SCLC by BN antagonist RC-3095 is accompanied by a decrease in the no. of receptors for both BN/GRP and EGF. These observations are in agreement with the results obtained in other exptl. cancers. The findings on antagonist RC-3095 reinforce the view that both BN/GRP and EGF receptors participate in a cascade of events involved in the growth of SCLC and other cancers. Although the complete mechanisms of action of antagonist RC-3095 remain to be elucidated, the antitumor effect could be the result of the fall in the EGF receptor no., which might lead to a decrease in EGF receptor autophosphorylation.

IT **138147-78-1**, RC-3095
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(redn. in receptors for bombesin and epidermal growth factor in xenografts of human small-cell lung **cancer** after treatment with bombesin antagonist RC-3095)

L7 ANSWER 5 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:580851 HCAPLUS
DOCUMENT NUMBER: 125:237839
TITLE: Effects of new bombesin antagonists given singly or in combination with a somatostatin analog on nitrosamine-induced pancreatic cancers in hamsters
AUTHOR(S): Szepeshazi, Karoly; Schally, Andrew V.; Cai, Ren-Zhi; Halmos, Gabor; Groot, Kate
CORPORATE SOURCE: Veterans Affairs Medical Center, Polypeptide and Cancer Institute, New Orleans, LA, 70146, USA
SOURCE: Int. J. Oncol. (1996), 9(3), 397-403
CODEN: IJONES; ISSN: 1019-6439
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In three expts., hamsters with N-nitrosobis(2-oxopropyl)amine-induced pancreatic cancers were treated for two months with bombesin/GRP antagonists RC-3095 [D-Tpi6, Leu13.psi.(CH2NH)Leu14-bombesin(6-14)], RC-3910-II [D-Tpi6, Leu13.psi.(CH2N)Tac14-bombesin(6-14)], RC-3940-II [Hca6, Leu13.psi.(CH2N)Tac14-bombesin(6-14)], RC-3950-II [D-Phe6,

Leu13.psi.(CH2N)Tac14-bombesin(6-14)], somatostatin analog RC-160 (D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH2), or the combination of RC-3095 with RC-160. All peptides inhibited pancreatic cancers to various degrees, reducing the no. of tumorous animals, lowering the wt. of tumorous pancreata by 40-55% and decreasing AgNOR nos. which are indicators of cell proliferation rate. Combination therapy with RC-3095 and RC-160 did not inhibit tumors better than single peptides. Among new bombesin/GRP antagonists, RC-3940-II had the strongest inhibitory effect. RC-3950-II and RC-3095 caused similar inhibition, but RC-3910-II was less effective. Tumor inhibitory activity of the bombesin/GRP antagonists was correlated with their binding affinities to bombesin receptors on tumor cells. RC-3940-II caused 50% inhibition of specific binding of [125I=Tyr4]bombesin to tumor cell membranes at 0.96 nM concn., while the IC50 for RC-3950-II was 5.27 nM and 12.94 nM for RC-3095. Our findings suggest that in addn. to RC-3095, other bombesin/GRP antagonists such as RC-3950-II and esp. RC-3940-II could be further developed for therapy of human pancreatic cancer.

IT **138147-78-1**, RC-3095 **166774-43-2**, RC-3910-II
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of bombesin antagonists and somatostatin analog on pancreatic **cancers**)

L7 ANSWER 6 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:204166 HCAPLUS
DOCUMENT NUMBER: 124:283275
TITLE: Bombesin antagonist prevents CO2 laser-induced promotion of oral cancer
AUTHOR(S): Kozacko, Mark F.; Mang, Thomas S.; Schally, Andrew V.; Priore, Roger L.; Liebow, Charles
CORPORATE SOURCE: Department Oral Maxillofacial Surgery, State University New York, Buffalo, NY, 14214, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1996), 93(7), 2953-7
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We previously reported that CO2 laser incisions in carcinogen-initiated fields promoted cancer development and caused release of growth factors. Here we examd. the quant. and additive properties of this tumor-promoting event and examd. whether this promotion could be nullified by treatment with a bombesin antagonist, which down-regulates epidermal growth factor receptors. The model used for cancer promotion was the hamster buccal cheek pouch that had been treated with a carcinogen (9,10-dimethyl-1,2-benzanthracene) for 6 wk, producing premalignant lesions. These lesions would evolve into a cancer eventually without further treatment. Promotion was measured both by increased fluorescence in response to systemically administered Photofrin, measured noninvasively using an in vivo fluorescence photometer, and by the timing of appearance of clin. tumors. Laser incisions (0-3) were made into the hamster cheek 1 wk apart, or three incisions were done 1 day apart. Another group of animals received bombesin antagonist RC-3095 for 4 wk during the time incisions were made, again measuring promotion. Laser incisions 1 wk apart produced additive promotion, whereas three incisions 1 day apart were not statistically different from the group receiving only one incision. RC-3095 treatment completely eliminated the promoting effects of incision and totally stopped promotion for the 4-wk period of treatment. After discontinuing treatment with RC-3095, lesion progression resumed at the untreated control rate. This work confirms that the promoting event of a laser incision follows a comparable time course to release of growth factors after such an incision and that it can be eliminated by treatment with bombesin antagonists.

IT **138147-78-1**, RC-3095
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bombesin antagonist prevents CO2 laser-induced promotion of oral **cancer**)

L7 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:670803 HCAPLUS
DOCUMENT NUMBER: 123:131996
TITLE: New pseudononapeptide bombesin antagonists with C-terminal Leu.psi.(CH2N)Tac-NH2 show high binding affinity to bombesin/GRP receptors on CFPAC-1 human pancreatic cancer cells
AUTHOR(S): Cai, Ren-Zhi; Qin, Yunfeng; Ertl, Tibor; Schally, Andrew V.
CORPORATE SOURCE: Veterans Affairs Medical Center, Endocrine, Polypeptide and Cancer Institute, New Orleans, LA, USA
SOURCE: Int. J. Oncol. (1995), 6(6), 1165-72
CODEN: IJONES; ISSN: 1019-6439
DOCUMENT TYPE: Journal
LANGUAGE: English
AB It has been demonstrated that bombesin/GRP antagonist D-Tpi6,Leu13.psi.(CH2NH) Leu14-BN(6-14) (RC-3095) inhibits effectively the growth of pancreatic cancer and other tumors in exptl. animals and in cell cultures. In an attempt to develop antagonists with still greater antitumor activity, several new pseudononapeptide bombesin/GRP antagonists contg. C-terminal Leu.psi.(CH2N)Tac-NH2 have been synthesized in our lab. In this study, we investigated the ability of four Leu13.psi.(CH2N)Tac14-BN(6-14) antagonists to inhibit the binding of bombesin to specific receptors for bombesin/GRP on CFPAC-1 human pancreatic cancer cells. Receptor binding assays were performed by incubating CFPAC-1 cells (5.times.104 cells/well) with 0.5 nM [125I]-Tyr4-bombesin in the absence or presence of (1 pM to 10 .mu.M) unlabeled bombesin, GRP (14-27) and various antagonists for 2 h at 22.degree.C. Displacement assays showed that antagonist D-Tpi6,Leu13.psi.(CH2N)Tac14-BN(6-14) (RC-3910-II) with a similar structure to RC-3095, but a different C-terminal, had a binding affinity to CFPAC-1 cells 15 times higher than RC-3095. Three other antagonists, RC-3925-II, RC-3940-II and RC-3950-II contained the same C-terminal Leu.psi.(CH2N)Tac-NH2 as RC-3910-II, but had different N-terminal residues: D-Cpa, Hca and D-Phe, resp. Among them, Hca6,Leu13.psi.(CH2N)Tac14-BN(6-14) (RC-3940-II) showed the highest binding affinity to the receptors on CFPAC-1 cells, which was 50 times higher than that of RC-3095 or 3 times greater than RC-3910-II. Our findings suggest the merit of further investigation of pseudononapeptide bombesin/GRP antagonist RC-3940-II and related analogs for a possible development of a new hormonal therapy for pancreatic cancer.
IT **138147-78-1**, RC-3095 **166774-43-2**, RC 3910-II
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new pseudononapeptide bombesin antagonists with C-terminal Leu.psi.(CH2N)Tac-NH2 show high binding affinity to bombesin/GRP receptors on CFPAC-1 human pancreatic **cancer** cells)

L7 ANSWER 8 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:633574 HCAPLUS
DOCUMENT NUMBER: 123:48011
TITLE: Development of a radioimmunoassay for a pseudononapeptide bombesin/GRP antagonist with antitumor activity
AUTHOR(S): Groot, Kate; Horvath, Judit E.; Cai, Ren-Zhi; Schally, Andrew V.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Inst., Veterans Affairs Medical Center, New Orleans, LA, USA
SOURCE: Int. J. Pept. Protein Res. (1995), 45(6), 561-6
CODEN: IJPPC3; ISSN: 0367-8377
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Bombesin-like and GRP-like peptides may act as autocrine growth factors in the proliferation of some cancers. A pseudononapeptide bombesin antagonist, [D-Trp6,Leu13.psi.(CH2NH)-Leu14]bombesin(6-14), and related analogs synthesized in the lab. significantly inhibit tumor growth in

various cancer models. A RIA, suitable for detn. of RC-3095 and its congeners in unextd. serum, was developed to facilitate further exptl. and clin. evaluation of this bombesin/GRP receptor antagonist for the treatment of various tumors. Antibodies were generated against RC-3095 and Des-Tpi1-RC-3095, conjugated to bovine serum albumin with glutaraldehyde. Antiserum JH-631b was selected for further expts. based on the antibody characterization. At an antiserum diln. of 1:189,000, this antibody bound .apprx.50% of 7 fmol of added radiolabeled Tyr1-RC-3095. The antibody cross-reacted with C-terminal fragments of RC-3095. Fragments without the C-terminus and naturally existing peptides of the bombesin family or structurally unrelated peptides did not cross-react. The min. detectable dose of RC-3095 was 0.4 pg/tube. Intra- and interassay coeffs. of variation ranged from 3.2 to 4.4% and from 5.6 to 12.8%, resp. The RIA is suitable for direct detn. of RC-3095 in serum. The RIA should be of value for monitoring levels of this analog in serum during long-term therapy.

IT **138147-78-1**, RC 3095
RL: ANT (Analyte); ANST (Analytical study)
(RIA of blood serum content of pseudononapeptide bombesin/GRP antagonist with **antitumor** activity)

L7 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:432974 HCAPLUS
DOCUMENT NUMBER: 122:255644
TITLE: Inhibitory effect of bombesin/gastrin-releasing peptide (GRP) antagonists RC-3950-II and RC-3095 on MCF-7 MIII human breast cancer xenografts in nude mice
AUTHOR(S): Shirahige, Y; Cai, R-Z; Szepeshazi, K; Halmos, G; Pinski, J; Groot, K; Schally, AV
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, New Orleans, LA, 70146, USA
SOURCE: Biomed. Pharmacother. (1994), 48(10), 465-72
CODEN: BIPHEX; ISSN: 0753-3322
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bombesin/gastrin-releasing peptide (GRP) may be involved in the growth of human breast cancers. Nude mice bearing xenografts of MCF-7 MIII human breast cancer cell line were treated for 7 wk with bombesin/GRP antagonists RC-3950-II and RC-3095. RC-3950-II, administered s.c. twice daily at a dose of 10 .mu.g, produced significant inhibitory effects on tumor growth after 2 wk of administration. RC-3095 acetate (D 22213), injected s.c. twice daily at the same dose of 10 .mu.g, suppressed tumor growth after 4 wk. Both RC-3950-II and RC-3095 significantly decreased the final tumor vol. and tumor wts. RC-3950-II appeared to be somewhat more efficacious than RC-3095 in inhibiting the growth of MCF-7 MIII breast cancers. Chronic treatment with either bombesin/GRP antagonist caused downregulation of receptors for epidermal growth factor (EGF) in tumor cell membranes, which might be related to inhibition of tumor growth. These findings suggest that bombesin/GRP antagonists should be considered for a new endocrine therapy of breast cancer.

IT **138147-78-1**, RC-3095 **162666-31-1**, D 22213
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antitumor** effect of bombesin/gastrin-releasing peptide antagonists RC-3950-II and RC-3095 on human breast **cancer**)

L7 ANSWER 10 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:401389 HCAPLUS
DOCUMENT NUMBER: 122:177845
TITLE: Bombesin antagonists inhibit in vitro and in vivo growth of human gastric cancer and binding of bombesin to its receptors
AUTHOR(S): Qin, Yunfeng; Halmos, Gabor; Cai, Ren-Zhi; Szoke, Balazs; Ertl, Tibor; Schally, Andrew V.
CORPORATE SOURCE: Veterans Affairs Medical Center, Endocrine Polypeptide and Cancer Institute, New Orleans, LA, 70146, USA
SOURCE: J. Cancer Res. Clin. Oncol. (1994), 120(9), 519-28

CODEN: JCROD7; ISSN: 0171-5216
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We investigated the effect of bombesin/gastrin releasing peptide (GRP) antagonist RC-3095 and other analogs on the growth of Hs746T human gastric cancer cells implanted in nude mice or cultured in vitro and on the binding of bombesin to its receptors. Nude mice bearing xenografts of the Hs746T cell line received s.c. injections of RC-3095 (10 .mu.g twice daily) or the vehicle (control) for 21 days. Administration of antagonist RC-3095 inhibited the growth of Hs746T tumors. Treatment with RC-3095 produced a significant decrease in tumor vol., prolonged the tumor vol. doubling time from 3.6 days to 5.1 days, and decreased the tumor growth rate by 76.9%. The tumor growth delay time in mice treated with RC-3095 was 2.8 days. Treatment with RC-3095 also decreased the final tumor wt. by 88.3% and reduced DNA and protein contents in tumors by 91.5% and 89.5%, resp., as compared to controls. The presence of specific receptors for bombesin/GRP was investigated on the crude membranes of implanted tumors of Hs746T cells. Satn. binding assays showed that the binding of [125I-Tyr4]bombesin to the membranes was saturable and reversible. Scatchard anal. indicated the presence of a single class of binding sites with a high affinity (Kd = 0.24 .+-. 0.07 nM) and a low binding capacity (Bmax = 57.0 .+-. 0.9 fmol/mg protein). In displacement studies, the binding of [125I-Tyr4]bombesin was inhibited in a dose-dependent manner by unlabeled bombesin(1-14), [Tyr4]-bombesin and GRP (14-27), but not by structurally unrelated peptides. Synthetic bombesin/GRP antagonists RC-3095, RC-3110, and RC-3950-II were all able to inhibit effectively the binding of [125I-Tyr4]bombesin to the membranes of Hs746T cells. RC-3950-II showed a higher binding affinity for bombesin receptors than RC-3095 or RC-3110. Addn. of the non-hydrolyzable guanine-nucleotide analog GTP [S] to the binding buffer caused a significant redn. in the amt. of [125I-Tyr4]bombesin bound to the cells, indicating that the bombesin receptor is coupled to a G-protein. In cell cultures, bombesin significantly stimulated the growth of Hs746T cells in vitro as shown by an increase in the uptake of [3H]thymidine. Bombesin antagonist RC-3095 could effectively inhibit the bombesin-stimulated growth of Hs746T cells in cultures. These observations suggest that bombesin/GRP may act as growth factors through specific receptors present on the membranes of Hs746T cells. Bombesin/GRP antagonists appear to nullify the effects of bombesin/GRP and may be useful for the treatment of gastric cancers.

IT **138147-78-1**, RC-3095
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bombesin antagonist RC-3095 inhibition of human gastric **cancer** growth and bombesin binding to its receptors)

L7 ANSWER 11 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:278612 HCAPLUS
DOCUMENT NUMBER: 123:9930
TITLE: Polypeptide bombesin antagonists
INVENTOR(S): Schally, Andrew V.; Cai, Renzhi
PATENT ASSIGNEE(S): The Administrators of the Tulane Educational Fund, USA
SOURCE: U.S., 36 pp. Cont.-in-part of U.S. 5,244,883.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5369094	A	19941129	US 1993-31325	19930315
US 5244883	A	19930914	US 1990-619747	19901129
CA 2097192	AA	19920530	CA 1991-2097192	19911115
HU 64566	A2	19940128	HU 1993-1567	19911115
HU 213114	B	19970228		
AT 120760	E	19950415	AT 1992-900740	19911115

ES 2072137	T3	19950701	ES 1992-900740	19911115
ZA 9109387	A	19920930	ZA 1991-9387	19911128
WO 9421674	A1	19940929	WO 1994-US2511	19940307
W: AU, BR, BY, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SI, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2135787	AA	19940929	CA 1994-2135787	19940307
CA 2157871	AA	19940929	CA 1994-2157871	19940307
AU 9464446	A1	19941011	AU 1994-64446	19940307
AU 666270	B2	19960201		
EP 646127	A1	19950405	EP 1994-912199	19940307
EP 646127	B1	19980701		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07507330	T2	19950810	JP 1994-521091	19940307
HU 69727	A2	19950928	HU 1994-3244	19940307
AT 167874	E	19980715	AT 1994-912199	19940307
ES 2120615	T3	19981101	ES 1994-912199	19940307
ZA 9401767	A	19941006	ZA 1994-1767	19940314
NO 9404293	A	19950102	NO 1994-4293	19941110
FI 9405378	A	19941115	FI 1994-5378	19941115
PRIORITY APPLN. INFO.:			US 1990-619747	19901129
			US 1993-31325	19930315
			WO 1994-US2511	19940307

OTHER SOURCE(S): MARPAT 123:9930

AB Pseudopeptides comprising a peptide of formula I: X-A1-A2-Trp-Ala-Val-Gly-His-Leu-.psi.-A9-Q wherein X is hydrogen, a single bond linking the .alpha. amino group of A1 to the .gamma. carboxyl moiety on the 3-propionyl moiety of A2 when A2 is Glu, or a group of formula R1CO wherein R1 is selected from the groups consisting of:. (A) hydrogen, C1-10-alkyl, Ph or phenyl-C1-10-alkyl, p-HI-Ph, p-HI-phenyl-C1-10-alkyl, naphthyl, naphthyl-C1-10-alkyl, indolyl, indolyl-C1-10-alkyl, pyridyl, pyridyl-C1-10-alkyl, thienyl, thienyl-C1-10-alkyl, cyclohexyl or cyclohexyl-C1-10-alkyl, where HI = F, Cl, Br, OH, CH3 or OCH3;. (B) N(R2)(R3), wherein R2 is hydrogen, C1-10 alkyl, Ph or phenyl-C1-10-alkyl, R3 is hydrogen or C1-10 alkyl;. (C) R4O, wherein R4 is C1-10 alkyl, Ph or phenyl-C1-10 -alkyl; A1 is a D- or L- amino acid residue selected from the group consisting of Phe, p-HI-Phe, pGlu, Nal, Pal, Tpi, unsubstituted Trp or Trp substituted in the benzene ring by one or more members selected from the group consisting of F, Cl, Br, NH2 or C1-3 alkyl; or A1 is a peptide bond linking the acyl moiety of R1CO to the .alpha. amino moiety of A2 ; A2 is Gln, Glu[--], Glu(Y) or His, wherein [--] is a single bond linking the .gamma. carboxyl group of A2 when A2 is Glu with the .alpha. amino group of A1 where X is a single bond, Y is OR5 or N(R5)(R6) wherein R5 is hydrogen, C1-3 alkyl or phenyl; R6 is hydrogen or C1-3 alkyl; and R7 is hydrogen, C1-3 alkyl or NHCONH2 ; Leu-.psi. is a reduced form of Leu wherein the C:O moiety is instead CH2 such that the bond of this CH2 moiety with the .alpha. amino group of the adjacent A9 residue is a pseudopeptide bond; A9 is Tac, MTac or DMTac; and Q is NH2 or OQ1 where Q1 is hydrogen, C1-10 alkyl, Ph or phenyl-C1-10 -alkyl; and the pharmaceutically acceptable acids or salts thereof. Inhibition of binding of 125I-Tyr4-bombesin to Swiss 3T3 cells by bombesin antagonists: Ki (nM) from <0.001 to 213. The effects of treatment with bombesin antagonists on tumor vol. of estrogen independent MXT mouse mammary cancers, human small cell lung carcinoma in nude mice, MIA PACA-2 pancreatic cancer tumors, and CAPAN-2 human pancreatic cancer were also reported.

IT **143491-06-9P 163759-26-0P 163759-34-0P**
163759-38-4P 163878-59-9P 163878-60-2P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(polypeptide bombesin antagonists as **neoplasm** inhibitors)

IT **163759-36-2DP**, resin bound **163878-62-4DP**, resin bound
RL: SPN (Synthetic preparation); PREP (Preparation)
(polypeptide bombesin antagonists as **neoplasm** inhibitors)

L7 ANSWER 12 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:236063 HCAPLUS

DOCUMENT NUMBER: 122:122615
TITLE: Effects of somatostatin analog RC-160 and bombesin/gastrin-releasing peptide antagonists on the growth of human small-cell and non-small-cell lung carcinomas in nude mice
AUTHOR(S): Pinski, J.; Schally, A.V.; Halmos, G.; Szepeshazi, K.; Groot, K.; O'Byrne, K.; Cai, R.-Z.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, New Orleans, LA, 70146, USA
SOURCE: Br. J. Cancer (1994), 70(5), 886-92
CODEN: BJCAAI; ISSN: 0007-0920
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We investigated the effects of our synthetic bombesin/gastrin-releasing peptide (GRP) antagonists and somatostatin analog RC-160 on the growth of human small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (non-SCLC) lines in nude mice. Athymic nude mice bearing xenografts of the SCLC NCI-H69 line or non-SCLC NCI-H157 line were treated for 5 and 4 wk, resp., with somatostatin analog RC-160 or various bombesin/GRP antagonists. RC-160, administered s.c. peritumorally at a dose of 100 .mu.g per animal per day, inhibited the growth of H69 SCLC xenografts as shown by more than 70% redn. in tumor vols. and wts., as compared with the control group. Bombesin/GRP antagonists, RC-3440, RC-3095 and RC-3950-II, given s.c. peritumorally at a dose of 20 .mu.g per animal per day, also inhibited the growth of H69 SCLC tumors. RC-3950-II had the greatest inhibitory effect and decreased tumor vol. and wts. by more than 80%. The growth of H-157 non-SCLC xenografts was significantly reduced by treatment with RC-160, but not with bombesin/GRP antagonist RC-3095. In mice bearing either tumor model, administration of RC-160 significantly decreased serum growth hormone and gastrin levels. Specific high-affinity receptors for bombesin and somatostatin were found on membranes of SCLC H69 tumors, but not on non-SCLC H157 tumors. Receptor analyses demonstrated high-affinity binding sites for epidermal growth factor (EGF) and insulin-like growth factor I (IGF-I) on the membranes of H69 and H157 tumors. EGF receptors were down-regulated on H69 tumors after treatment with RC-160 and bombesin/GRP antagonists. The concn. of binding sites for EGF and IGF-I on the H157 tumors was decreased after treatment with RC-160, but bombesin/GRP antagonist RC-3095 had no effect. These results demonstrate that bombesin/GRP antagonists inhibit the growth of H-69 SCLC, but not of H-157 non-SCLC xenografts in nude mice, whereas somatostatin analog RC-160 is effective in both tumor models. This raises the possibility that these peptide analogs could be used selectively in the treatment of various subclasses of lung cancer.

IT **138147-78-1**, RC-3095 **142824-94-0**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(somatostatin analog RC-160 and bombesin/gastrin-releasing peptide antagonists RC-3440, RC-3095, and RC-3950-II **antitumor** effect on human small-cell and non-small-cell lung carcinoma)

L7 ANSWER 13 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:222483 HCAPLUS
DOCUMENT NUMBER: 122:24089
TITLE: Combination treatment of nitrosamine-induced pancreatic cancers in hamsters with analogs of LH-RH and a bombesin/GRP antagonist
AUTHOR(S): Szepeshazi, Karoly; Halmos, Gabor; Groot, Kate; Schally, Andrew V.
CORPORATE SOURCE: Endocrine, Polypeptide, and Cancer Institute, Veterans Affairs Medical Center, New Orleans, LA, 70146, USA
SOURCE: Int. J. Pancreatol. (1994), 16(2-3), 141-9
CODEN: IJPNEX; ISSN: 0169-4197
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Analogs of LH-releasing hormone (LH-RH) and bombesin/gastrin-releasing peptide were previously shown to inhibit the growth of exptl. pancreatic

cancers. In the present study, to increase the efficacy of therapy, female Syrian golden hamsters with N-nitrosobis(2-oxopropyl)amine-induced pancreatic cancers were treated for 2 mo with a combination of LH-RH agonist [D-Trp6]LH-RH or antagonist [Ac-D-Nal(2)1,D-Phe(4Cl)2,D-Pal(3)3,D-Cit6-Ala10]LH-RH (SB-75) and bombesin/GRP antagonist D-Tpi6,Leu13.psi.(CH2NH)Leu14bombesin(6-14) (RC-3095). The results were compared to those obtained by treatment with same doses of single peptides. LH-RH analogs and bombesin antagonist given alone significantly reduced the no. of tumorous animals and decreased wt. of pancreata by 46-71% and wt. of tumorous pancreas by 38-64%. Histol. showed lower mitotic activity and a decreased no. of AgNORs in tumor cells from treated animals. Enhanced apoptosis was also obsd. after treatment with the LH-RH analogs. Combination therapy had no superior inhibitory effect on tumors compared to single peptides, by practically all the parameters analyzed. The reasons for this lack of potentiation are not clear. The tumor inhibitory effect of bombesin antagonists appears to be mediated by interference with EGF-receptor mechanisms. In the present study, although a significant downregulation of EGF-receptors was found in tumors treated with combination, the decrease in binding capacity for EGF was maximal in the group treated with RC-3095 alone. Since intracellular signaling mechanisms are common for LH-RH and bombesin-like peptides, it is possible that second messengers were already maximally utilized by treatment with single peptides. Bombesin/GRP abolished the apoptosis enhancing effect of the LH-RH analogs, probably by interference in intracellular mechanisms. A more complete elucidation of the exact mechanisms of action of LH-RH and bombesin/GRP analogs is necessary for planning a successful combination therapy with these peptides.

IT **138147-78-1**, RC-3095
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pancreatic **cancer** treatment in hamsters with analogs of LH-RH and bombesin GRP antagonist)

L7 ANSWER 14 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:596444 HCAPLUS
DOCUMENT NUMBER: 121:196444
TITLE: Characterization of high-affinity receptors for bombesin/gastrin releasing peptide on the human prostate cancer cell lines PC-3 and DU-145: internalization of receptor bound 125I-[Tyr4]bombesin by tumor cells
AUTHOR(S): Reile, Herta; Armatis, Patricia E.; Schally, Andrew V.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, New Orleans, LA, 70146, USA
SOURCE: Prostate (N. Y.) (1994), 25(1), 29-38
CODEN: PRSTDS; ISSN: 0270-4137
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Specific receptors for bombesin/gastrin releasing peptide (GRP) on the androgen-independent human prostate cancer cell lines PC-3 and DU-145 were characterized. No specific binding of 125I-[Tyr4]bombesin to the androgen-dependent human prostate cancer cell line LNCaP was detectable. The binding of 125I-[Tyr4]bombesin to PC-3 and DU-145 cells was time- and temp.-dependent, saturable, and reversible. Scatchard anal. revealed a single class of binding sites with high affinity (Kd 9.8.times.10-11M for PC-3, and 9.1.times.10-11M for DU-145 cells at 25.degree.) and with a binding capacity of 44,000 binding sites/cell and 19,000 binding sites/cell, resp. Bound 125I-[Tyr4]bombesin was rapidly internalized by PC-3 cells. The nonhydrolyzable GTP analog GTP-.gamma.-S caused a dose-dependent inhibition of 125I-[Tyr4]bombesin binding to PC-3 and DU-145 cells, indicating that a G-protein couples the bombesin receptor to intracellular effector systems. Bombesin and GRP(14-27) inhibited the binding of 125I-[Tyr4]-bombesin to both cell lines in a dose-dependent manner with inhibition consts. (Ki) of 0.5 nM and 0.4 nM, resp. Both cell lines express the bombesin/GRP-preferring bombesin receptor subtype, since, in displacement studies, neuromedin B was >200-fold less potent than bombesin and GRP(14-27) in inhibiting the binding of

125I-[Tyr4]bombesin. Two synthetic bombesin/GRP antagonists, RC 3095 and RC 3110, powerfully inhibited the specific binding of 125I-[Tyr4]bombesin with Ki 0.92 nM and 0.26 nM on PC-3 cells, and 3.3 nM and 0.89 nM on DU-145 cells, resp. Apparently, the PC-3 and DU-145 human prostate cancer cell lines possess specific high-affinity receptors for bombesin/GRP, and are suitable models for the evaluation of the antineoplastic activity of new bombesin/GRP antagonists in the treatment of androgen-independent prostate cancer.

IT **138147-78-1**, RC 3095
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bombesin binding to human prostate **cancer** cell lines PC-3 and DU-145 inhibition by)

L7 ANSWER 15 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:474291 HCAPLUS
DOCUMENT NUMBER: 121:74291
TITLE: Characterization of a bombesin/gastrin-releasing peptide receptor on a human gastric-cancer cell line
AUTHOR(S): Preston, Shaun R.; Woodhouse, Linda F.; Gokhale, Jay; Miller, Glenn V.; Primrose, John N.
CORPORATE SOURCE: Academic Unit Surgery, St. James's University Hospital, Leeds, LS9 7TF, UK
SOURCE: Int. J. Cancer (1994), 57(5), 734-41
CODEN: IJCNAW; ISSN: 0020-7136
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study examd. the expression of receptors of the bombesin (BBS) family in human gastric-cancer cell lines. Of 5 cell lines screened, only one, St42, demonstrated specific binding sites for 125I-Tyr4-BBS, which have been further characterized. This binding was saturable, and temp.- and time-dependent. Scatchard anal. of displacement data performed at 37.degree. revealed 2 binding sites: a high-affinity, low-capacity site (KD = 0.13 nM, Bmax = 1500 sites/cell) and a lower-affinity, higher-capacity site (KD = 11 nM, Bmax = 35,000 sites/cell); the latter was lost when internalization of peptide was prevented, suggesting that it may be an artifact. Displacement assays with gastrin-releasing peptide (GRP) and neuromedin B (NMB) revealed that the receptor was of the GRP-preferring sub-type (GRP IC50 = 0.35 nM; NMB IC50 = 112 nM). Co-valent crosslinking of 125I-Tyr4-BBS to the receptor demonstrated the presence of a single band corresponding to a mol. wt. of 37 to 44 kDa on SDS-PAGE, similar to that of the cloned GRP receptor protein core. G-protein linkage of this receptor was demonstrated by selective inhibition of 125I-Tyr4-BBS binding by guanosine nucleotides. The binding of BBS to the receptor resulted in a rise in intracellular calcium. Three of four structurally distinct BBS antagonists bound to the receptor with high affinity, but [DPhe12, Leu14]-bombesin did not cause any displacement of 125I-Tyr4-BBS even at 10 mM. The functional significance of GRP receptors on human gastric-cancer cells is as yet unknown, but further studies may det. whether such receptors have importance in the therapy of gastric cancer.

IT **138147-78-1**, RC-3095
RL: BIOL (Biological study)
(gastrin-releasing peptide receptor affinity for, of human gastric **cancer** cells)

L7 ANSWER 16 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:450450 HCAPLUS
DOCUMENT NUMBER: 121:50450
TITLE: Inhibitory effect of bombesin/gastrin-releasing peptide antagonist RC-3095 and luteinizing hormone-releasing hormone antagonist SB-75 on the growth of MCF-7 MIII human breast cancer xenografts in athymic nude mice
AUTHOR(S): Yano, Tetsu; Pinski, Jacek; Szepeshazi, Karoly; Halmos, Gabor; Radulovic, Sinisa; Groot, Kate;

Schally, Andrew V.
CORPORATE SOURCE: Veterans Aff. Med. Cent., Endocr. Polypept. and Cancer Inst., New Orleans, LA, USA
SOURCE: Cancer (Philadelphia) (1994), 73(4), 1229-38
CODEN: CANCAR; ISSN: 0008-543X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The results of several clin. trials using various LH-releasing hormone agonists for treatment of advanced breast cancer are encouraging. However, only about 30% of breast cancers are estrogen-dependent and can be treated by hormonal manipulation. New therapeutic approaches combining estrogen ablation therapy with other compds. must be explored. Various studies suggest that bombesin or gastrin-releasing peptide acts as an autocrine growth factor and may play a role in the initiation and progression of some cancers, including that of the breast. Female athymic nude mice bearing xenografts of the MCF-7 MIII human breast cancer cell line were treated for 7 wk with bombesin/gastrin-releasing peptide antagonist (D-Tpi6, Leu13 .PSI.[CH2NH]-Leu14) bombesin (6-14) (RC-3095) injected s.c. daily at a dose of 20 .mu.g and LH-releasing hormone antagonist SB-75 (Cetrorelix) administered biweekly in the form of microgranules releasing 45 .mu.g/day. After 2 wk of treatment, a significant inhibition of tumor vol. was obsd. in the groups treated with RC-3095 alone or in combination with SB-75 but not in those treated with SB-75 as a single agent. After 7 wk, tumor growth as measured by tumor vol. and percentage changes in tumor vol. and tumor wt. was greatly inhibited in all of the treated groups. Uterine and ovarian wts. were reduced and serum LH levels decreased by administration of SB-75 alone or in combination with RC-3095. Histol., a significant decrease in argyrophilic nucleolar organizer region count in tumor cell nuclei was obsd. in all of the treated groups, indicating a lower proliferation of these cells. High-affinity binding sites for bombesin were detected in cultured MCF-7 MIII cells. Chronic treatment with RC-3095 caused a significant down-regulation of epidermal growth factor receptors in tumor cell membranes, which might be related to tumor inhibition. In studies in vitro, SB-75 inhibited proliferation of MCF-7 cells in culture but not proliferation of MCF-7 MIII cells. Because previously the authors demonstrated that RC-3095 inhibits the proliferation of MCF-7 MIII cells in vitro, it appears that the major antitumoral effect of RC-3095 on the MCF-7 MIII cancer line is direct, whereas that of SB-75 is indirect, and that it is mediated by suppression of the pituitary-gonadal axis. In view of its immediate and powerful inhibitory effect on MCF-7 MIII tumors, bombesin/gastrin-releasing peptide antagonist RC-3095 might be considered as a possible new agent for the treatment of breast cancer.
IT **138147-78-1**, RC-3095
RL: BIOL (Biological study)
(breast **cancer** of humans inhibition by, in lab. animals, LHRH antagonist SB-75 effect on)

L7 ANSWER 17 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:290486 HCAPLUS
DOCUMENT NUMBER: 120:290486
TITLE: Synergistic effects of bombesin and epidermal growth factor on cancers
AUTHOR(S): Liebow, Charles; Crean, David H.; Lee, Ming T.; Kamer, Angela R.; Mang, Thomas S.; Schally, Andrew V.
CORPORATE SOURCE: Buffalo Gen. Hosp., State Univ. New York, Buffalo, NY, 14214, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1994), 91(9), 3804-8
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Bombesin and gastrin-releasing peptide act as autocrine mitogens in various cancers. Bombesin antagonist RC-3095 inhibited growth in some cancers and slowed the progression of premalignant lesions, possibly by down-regulating epidermal growth factor (EGF) receptors. Since the EGF receptor mitogen response involves tyrosine kinase stimulation, the

authors tested the hypotheses that bombesin stimulates, and RC-3095 inhibits, phosphorylation; EGF and bombesin promote the phosphorylation of the same substrates; and EGF and bombesin act synergistically on phosphorylation. Therefore, in vitro assays for phosphorylation were performed in the presence of absence of EGF, bombesin, RC-3095, and combinations in samples derived from tumor, tissue surrounding tumor, cell lines, and normal and transforming tissue derived from the 9,10-dimethyl-1,2-benzanthracene-induced squamous cell lesions of the hamster cheek pouch. Bombesin increased, and RC-3095 decreased, phosphorylation in these samples. In the human hepatoma sample and surrounding tissue, these ligands altered the phosphorylation of the same substrates affected by EGF. EGF and bombesin stimulated phosphorylation synergistically in the hamster samples and the hepatoma. Bombesin-induced phosphorylation was greater in tissue surrounding the hepatoma, whereas RC-3095 was more effective in inhibiting phosphorylation in the hepatoma itself. This cancer, therefore, could be endogenously stimulated by gastrin-releasing peptide. These observations support the hypothesis that bombesin stimulates growth of tissues and tumors by amplifying the phosphorylation response to EGF. The growth inhibitory response to RC-3095, or other bombesin analogs, of individual tumors may be prognosed by in vitro phosphorylation assays using the samples from the patient's tumor.

IT **138147-78-1**, RC-3095
RL: BIOL (Biological study)
(protein phosphorylation in response to, in **neoplasm**)

L7 ANSWER 18 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:209063 HCAPLUS
DOCUMENT NUMBER: 120:209063
TITLE: Inhibitory effect of bombesin receptor antagonist RC-3095 on the growth of human pancreatic cancer cells in vivo and in vitro
AUTHOR(S): Qin, Yunfeng; Ertl, Tibor; Cai, Ren Zhi; Halmos, Gabor; Schally, Andrew V.
CORPORATE SOURCE: Endocr. Polypept. Cancer Inst., Veterans Aff. Med. Cent., New Orleans, LA, 70146, USA
SOURCE: Cancer Res. (1994), 54(4), 1035-41
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this study, the authors investigated the effect of bombesin/GRP antagonist RC-3095 on the growth of CFPAC-1 human pancreatic cancer cells transplanted to nude mice or cultured in vitro. Nude mice bearing xenografts of the CFPAC-1 cell line received s.c. injections of RC-3095 (10 .mu.g twice a day) or the vehicle (control) for 25 days. Chronic administration of RC-3095 inhibited the growth of CFPAC-1 tumors in nude mice as shown by a significant decrease in tumor vol. throughout the period of treatment. Tumor vol. doubling time was prolonged by RC-3095 treatment from 7.2 days to 10 days, and the tumor growth rate was decreased by 49%. In mice treated with RC-3095, the tumor growth delay time was 5.8 days. Treatment with RC-3095 decreased the final tumor wt. by 37% and reduced DNA and protein contents in tumor tissues by 44 and 39.9%, resp., compared to the controls. In cultures of the CFPAC-1 cell line, the addn. of bombesin (1-14) (1 pM-0.1 .mu.M) to the medium induced a dose-dependent increase in cell no. RC-3095 at 1 nM concn. effectively inhibited the bombesin-stimulated growth of CFPAC-1 cells in cultures. In the presence of 1 .mu.Ml RC-3095 in the culture medium, the bombesin-induced growth of CFPAC-1 cells was totally suppressed. Bombesin was also shown to stimulate the DNA synthesis in CFPAC-1 cells in vitro as based on [3H]thymidine incorporation assay. When the cells were cultured in the presence of 1-100 nM bombesin, the uptake of [3H]thymidine by the cells was increased by 89-131%. RC-3095 inhibited both the basal and bombesin-stimulated DNA synthesis of CFPAC-1 cells. Addn. of RC-3095 (10-100 nM) alone to the cultures caused a 39-40% decrease in the [3H]thymidine incorporation by the cells. Concomitant addn. of RC-3095 (1 .mu.M) and bombesin (1-100 nM) to the cultures induced a significant redn.

in the uptake of [3H]thymidine by the cells compared to the values obtained with bombesin alone. Receptor binding assays showed the presence of two classes of specific binding sites for bombesin on CFPAC-1 cells, one with high affinity (Kd = 4.25 NM) and low capacity (Bmax = 0.268 pmol/106 cells) and and the other with low affinity (Kd = 321.70 nM) and high capacity (Bmax = 3.991 pmol/106 cells). Antagonist RC-3095 inhibited the binding of 125I-Tyr4-bombesin to CFPAC-1 cell membranes in a dose-dependent manner. These observations suggest that bombesin acts as a growth factor and stimulates proliferation of CFPAC-1 human pancreatic cancer through specific receptors for bombesin/GRP present on the cells. RC-3095 appears to inhibit the growth of CFPAC-1 cells by blocking the interaction of bombesin with its receptors. The bombesin/GRP receptor antagonist RC-3095 could be considered for the development of new approaches for treatment of human pancreatic cancers.

IT **138147-78-1**, RC-3095
RL: BIOL (Biological study)
(pancreas **cancer** inhibition by, as bombesin receptor antagonist, in human cells in lab. animals)

L7 ANSWER 19 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:70217 HCAPLUS
DOCUMENT NUMBER: 120:70217
TITLE: Inhibitory effects of somatostatin analog RC-160 and bombesin/gastrin-releasing peptide antagonist RC-3095 on the growth of the androgen-independent Dunning R-3327-AT-1 rat prostate cancer
AUTHOR(S): Pinski, Jacek; Reile, Herta; Halmos, Gabor; Groot, Kate; Schally, Andrew V.
CORPORATE SOURCE: Endocr. Polypept. Cancer Inst., Veterans Aff. Med. Cent., New Orleans, LA, 70146, USA
SOURCE: Cancer Res. (1994), 54(1), 169-74
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of somatostatin analog RC-160 and bombesin/gastrin releasing-peptide (GRP) antagonist RC-3095 were evaluated in Copenhagen rats bearing the anaplastic, androgen-independent Dunning R3327-AT-1 prostate adenocarcinoma. In the first expt., RC-160 was given in the form of microcapsules releasing 60 .mu.g/day/rat. RC-3095 was administered from implanted Alzet osmotic minipumps liberating 100 .mu.g/day/rat. After 32 days, tumor vols. and wts. were significantly reduced by RC-160 as compared with the control group. Tumor doubling time in rats treated with RC-160 was significantly longer than in controls. Bombesin/GRP antagonist RC-3095 also significantly reduced tumor vol. after 7 days of treatment, but after 18 days the inhibition in tumor vol. was no longer significant. Tumor growth was not suppressed by castration. In the 2nd expt., 3-mm3 fragments of Dunning R-3327-AT-1 tumor were implanted orthotopically into the prostates of Copenhagen rats to evaluate the survival time of animals bearing this cancer during treatment with RC-160 released from Alzet osmotic minipumps at a dose of 100 .mu.g/day/rat. Treatment with RC-160 significantly prolonged the mean survival time of rats by 5.3 days as compared to control animals. In both experimentals, therapy with RC-160 significantly decreased serum growth hormone or insulin-like growth factor I levels. In the first expt., receptor assays on R-3327-AT-1 tumor membranes showed high affinity binding sites for somatostatin, bombesin, and epidermal growth factor. At the end of the treatment, receptors for epidermal growth factor were significantly down-regulated by treatment with RC-160 but not with RC-3095. The binding capacity of bombesin receptors was reduced to nondetectable levels after the treatment with RC-3095. In cell cultures, high affinity binding sites for bombesin/GRP were found on intact Dunning R-3327-AT-1 cells, but receptors for somatostatin could not be detected. Proliferation of the AT-1 cell line was significantly inhibited by antagonist RC-3095. However, no effect on tumor cell growth in vitro was obsd. with analog RC-160. The authors' results demonstrate that somatostatin analog RC-160 and bombesin/GRP antagonist RC-3095 can inhibit the growth of the

androgen-independent Dunning R-3327-AT-1 prostatic cancer in rats, although the remission produced by RC-3095 may be of short duration due to a down-regulation of bombesin receptors. The authors' work suggests the merit of further investigation as to whether these analogs can induce a possible delay in relapse and prolong survival in prostate cancer.

IT **138147-78-1**, RC-3095
RL: BIOL (Biological study)
(Dunning R-3327-AT-1 prostate **cancer** response to)

L7 ANSWER 20 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:617846 HCAPLUS
DOCUMENT NUMBER: 119:217846
TITLE: Somatostatin analog RC-160 and bombesin/gastrin-releasing peptide antagonist RC-3095 inhibit the growth of androgen-independent DU-145 human prostate cancer line in nude mice
AUTHOR(S): Pinski, Jacek; Halmos, Gabor; Schally, Andrew V.
CORPORATE SOURCE: Endocrine, Polypeptide Cancer Inst., Veterans Aff. Med. Cent., New Orleans, LA, 70146, USA
SOURCE: Cancer Lett. (Shannon, Irel.) (1993), 71(1-3), 189-96
CODEN: CALEDQ; ISSN: 0304-3835
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Nude mice bearing xenografts of the androgen-independent human prostate cancer DU-145 were treated for 4-5 wk with somatostatin analog RC-160 or the bombesin/gastrin-releasing peptide (GRP) antagonist RC-3095. Tumor growth in animals treated with somatostatin analog RC-160 at a dose of 100 .mu.g/day s.c. was inhibited within 14 days of the start of the expt. At necropsy, in mice given RC-160, tumor wt. and vol. were decreased compared with control mice. Treatment with RC-3095 at a dose of 20 .mu.g/day s.c. also suppressed tumor growth, the inhibition being significant after 2 wk, but the redn. in tumor and wt. was smaller than that produced by RC-160. Therapy with RC-160 decreased serum GH and gastrin levels. Specific binding sites for bombesin, somatostatin and EGF were found in the Du-145 tumor membranes. Receptors for EGF were down-regulated after therapy with RC-3095 and RC-160. The finding that somatostatin analog RC-160 and bombesin/GRP antagonist RC-3095 inhibit the growth of androgen-independent prostate tumor in mice might be of practical importance for human prostate cancer therapy.

IT **138147-78-1**, RC-3095
RL: BIOL (Biological study)
(prostate **cancer** cell growth from human inhibition by, in mouse)

L7 ANSWER 21 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:552487 HCAPLUS
DOCUMENT NUMBER: 119:152487
TITLE: Effect of bombesin, gastrin-releasing peptide (GRP)(14-27) and bombesin/GRP receptor antagonist RC-3095 on growth of nitrosamine-induced pancreatic cancers in hamsters
AUTHOR(S): Szepeshazi, Karoly; Schally, Andrew V.; Groot, Kate; Halmos, Gabor
CORPORATE SOURCE: Endocrine, Polypeptide CAncer Inst., Veterans Affairs Med. Cent., New Orleans, LA, 70146, USA
SOURCE: Int. J. Cancer (1993), 54(2), 282-9
CODEN: IJCNAW; ISSN: 0020-7136
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Female Syrian golden hamsters with N-nitroso-bis(2-oxopropyl)amine (BOP)-induced pancreatic cancers were treated for 2 mo with bombesin/gastrin-releasing peptide (GRP) antagonist D-Tpi6, Leu13.psi.(CH2NH)Leu14 bombesin(6-14) (RC-3095). Bombesin and GRP(14-27) were also administered alone and in combination with the antagonist RC-3095. RC-3095 exerted a dose-dependent inhibitory effect on growth of pancreatic cancers. The no. of animals with pancreatic cancers was

significantly lower in the group treated with 60 .mu.g/day of RC-3095 and the wt. of tumorous pancreata was reduced. Administration of bombesin or GRP alone did not stimulate the growth of pancreatic tumors and, in fact, had a slightly suppressive effect on cancers. Bombesin and GRP(14-27) given together with RC-3095 did not nullify the inhibitory effect of the antagonist on pancreatic cancer growth. Actually, a greater inhibition of pancreatic tumors was obsd. after administration of RC-3095 together with bombesin or GRP, than with RC-3095 alone. The mechanism of action of bombesin, GRP, and bombesin antagonists on pancreatic cancers appears to be complex. The inhibitory effect of bombesin antagonists on pancreatic cancer growth was accompanied by a decrease in the binding capacity of EGF receptors in tumor membranes. Administration of bombesin also caused a down-regulation of EGF receptors, and the greatest decrease in binding capacity of EGF receptors was obsd. after treatment with RC-3095 in combination with GRP. Inhibition of pancreatic cancer can thus be tentatively explained by some common pathways in the action of bombesin, GRP and their antagonists, and these could be mediated by interference with EGF-receptor mechanisms.

IT **138147-78-1**, RC-3095
RL: BIOL (Biological study)
(**neoplasm**-inhibitory activity of, mechanism of)

L7 ANSWER 22 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:183952 HCAPLUS
DOCUMENT NUMBER: 118:183952
TITLE: Peptide analogs alter the progression of premalignant lesions, as measured by Photofrin fluorescence
AUTHOR(S): Liebow, Charles; Crean, David H.; Schally, Andrew V.; Mang, Thomas S.
CORPORATE SOURCE: Photodyn. Therapy Cent., Roswell Park Cancer Inst., Buffalo, NY, 14263, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1993), 90(5), 1897-901
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The somatostatin analog RC-160 and the bombesin/gastrin-releasing peptide antagonist RC-3095 were infused at 2 .mu.g/day via miniosmotic pumps implanted s.c. in hamsters with premalignant disease to examine the effect of these peptides on cancer promotion and progression. These analogs have been shown to inhibit growth of certain tumors, esp. those that overexpress tyrosine kinase activity. Progression of premalignant lesions initiated by applying 0.5% DMBA to the hamster buccal cheek pouch was measured by Photofrin-induced fluorescence 24 h after injecting the porphyrin (1.0 mg/kg) by using in vivo fluorescence photometry. This method of monitoring progression was reaffirmed by the observations that fluorescence increased as compared with controls in lesions receiving 4 addnl. weeks of continuous promotion by DMBA application and in lesions receiving transient promotion by laser incision. Twelve weeks after treatment, fluorescence had decreased among animals treated for 2 wk with RC-3095 (control, 0.53 vs. RC-3095, 0.28 vs. RC-160, 0.24). These data were obtained 20 wk after DMBA initiation. Thus, treatment with RC-160 and RC-3095 decreased the progression, measured by fluorescence, compared with control animals. In addn., there was also an abs. continuous decrease in fluorescence for the 22 wk after the cessation of RC-160 treatment. That the changes in tumor progression produced by RC-160 extended beyond the treatment period supports the hypothesis that the changes were irreversible. Histopathol. anal. revealed normal tissue and/or mild-moderate dysplasia in hamster buccal mucosa treated with the RC-160 (an improvement compared to pretreatment), whereas 40% of the animals receiving no treatment after DMBA initiation developed invasive squamous cell carcinomas after 20 wk. Evidently the antagonists of bombesin/gastrin-releasing peptide can delay the development of malignancies and the agonists of somatostatin can potentially reverse this development.

IT **138147-78-1**, RC-3095

RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**neoplasm** inhibition by)

L7 ANSWER 23 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:116348 HCAPLUS
DOCUMENT NUMBER: 118:116348
TITLE: Growth inhibition of estrogen-dependent and estrogen-independent MXT mammary cancers in mice by the bombesin and gastrin-releasing peptide antagonist RC-3095
AUTHOR(S): Szepeshazi, Karoly; Schally, Andrew V.; Halmos, Gabor; Groot, Kate; Radulovic, Sinisa
CORPORATE SOURCE: Endocr. Polypept. Cancer Inst., Veterans Aff. Med. Cent., New Orleans, LA, 70146, USA
SOURCE: J. Natl. Cancer Inst. (1992), 84(24), 1915-22
CODEN: JNCIEQ; ISSN: 0027-8874
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Antagonists of bombesin and gastrin-releasing peptide, including RC-3095, inhibit the growth of pancreatic, colonic, and prostatic cancers in exptl. animals. This effect is assocd. with a substantial decrease in EGF receptor levels in pancreatic and colon cancers. The effects of the synthetic bombesin and gastrin-releasing peptide receptor antagonist [D-Tpi6,Leu13.psi.(CH2NH)-Leu14]bombesin(6-14) (RC-3095) on the growth of hormone-dependent and hormone-independent MXT mouse mammary cancers were studied in vivo. Female mice bearing the MXT carcinomas were treated with small doses (20 .mu.g/day) of RC-3095 administered from osmotic minipumps. Groups of mice with estrogen-independent tumors received RC-3095, bombesin, or gastrin-releasing peptide(14-27) at 20 .mu.g/day. Tumor vol. and wt., mitotic index, apoptosis (programmed cell death), and argyrophilic nucleolar organizer regions were detd. as indicators of tumor cell proliferation. The levels of EGF receptors and bombesin were measured in tumor membrane fractions. The growth of both estrogen-dependent and estrogen-independent MXT cancers was inhibited by RC-3095. Bombesin or gastrin-releasing peptide had no effect on the growth of estrogen-independent tumors. In estrogen-independent cancers, the tumor inhibition was assocd. with a decrease in the capacity of EGF receptors from 0.21 to 0.03 pmol/mg membrane protein in control and RC-3095-treated groups, resp. Bombesin antagonists should be considered for breast cancer therapy.
IT **138147-78-1**, RC-3095
RL: PRP (Properties)
(**antitumor** effects of, in breast **cancer**, estrogen dependence in relation to)

L7 ANSWER 24 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1992:525018 HCAPLUS
DOCUMENT NUMBER: 117:125018
TITLE: Inhibition of growth of PC-82 human prostate cancer line xenografts in nude mice by bombesin antagonist RC-3095 or combination of agonist [D-Trp6]-luteinizing hormone-releasing hormone and somatostatin analog RC-160
AUTHOR(S): Milovanovic, Slobodan R.; Radulovic, Sinisa; Groot, Kate; Schally, Andrew V.
CORPORATE SOURCE: Endocr. Polypept. Cancer Inst., Veterans Adm. Med. Cent., New Orleans, LA, 70146, USA
SOURCE: Prostate (N. Y.) (1992), 20(4), 269-80
CODEN: PRSTDS; ISSN: 0270-4137
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The antitumor activity of bombesin antagonist RC-3095 and the combination of [D-Trp6]LH-RH and somatostatin analog RC-160 in human prostate cancer line xenografts in nude mice was investigated. The efficacy of the LH-RH and somatostatin analogs combination was greater than the therapeutic

effect of either analog alone. Addnl., results suggested that bombesin antagonists may be useful in the management of prostate carcinoma.

IT **138147-78-1**, RC 3095
RL: BIOL (Biological study)
(prostate **cancer** inhibition by, from human)

L7 ANSWER 25 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1992:483811 HCAPLUS
DOCUMENT NUMBER: 117:83811
TITLE: The binding of bombesin and somatostatin and their analogs to human colon cancers
AUTHOR(S): Radulovic, Sinisa S.; Milovanovic, Slobodan R.; Cai, Ren Zhi; Schally, Andrew V.
CORPORATE SOURCE: Cancer Inst., VA Med. Cent., New Orleans, LA, 70146, USA
SOURCE: Proc. Soc. Exp. Biol. Med. (1992), 200(3), 394-401
CODEN: PSEBAA; ISSN: 0037-9727
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Specific receptors for bombesin/gastrin-releasing peptide, somatostatin, and EGF were investigated in 15 human colon cancer specimens. Eight of 15 clin. specimens (15%) of colon cancer showed the presence of somatostatin receptors. Octapeptide somatostatin analogs, RC 160 and RC 121, showed 10 times higher binding affinity for somatostatin receptors on colon cancer membranes than did somatostatin. Anal. of 125I-Tyr4-bombesin binding data revealed the presence of specific binding sites in 6 (40%) specimens of human colon cancer. Scatchard anal. of 125I-labeled bombesin indicated a single class of receptors in 3 specimens with an apparent Kd value of 2.5 nM and 2 classes of receptors with high (Kd = 0.4 nM) and low affinity (Kd = 1.6 .mu.M) in 3 other specimens. The 125I-Tyr4-bombesin binding capacities in the colon cancers for high affinity binding sites were from 6 to 228 fmol/mg protein and for low affinity binding sites 76 pmol/mg protein. None of the membrane prepns. made from normal colonic mucosa specimens showed specific binding for 125I-Tyr4-bombesin. Five pseudononapeptide (.psi.13-14)bombesin-(6-14) antagonists, with different modifications at positions 6 and 14, synthesized in our lab., inhibited the binding of 125I-Tyr4-bombesin in nanomolar concns. No correlation was found between the degree of differentiation and the presence of binding sites for somatostatin or bombesin. Specific binding of EGF was detected in 80% of colon cancer specimens. EGF binding capacity in colon cancer membranes was on av. twice as high as in normal colon mucosa (50 vs. 28 fmol/mg protein, resp.). Specific binding sites for somatostatin and EGF, but not bombesin, were also demonstrated in human colon cancer cell line HT-29. In HCT-116 colon cancer line only EGF receptors were found. These receptor findings and in vivo studies on inhibition of colon cancer growth support the merit of continued evaluation of somatostatin analogs and bombesin/gastrin-releasing peptide antagonists in the management of colonic carcinoma.

IT **138147-78-1**, RC 3095
RL: PROC (Process)
(receptor binding of, in human colon **cancer**)

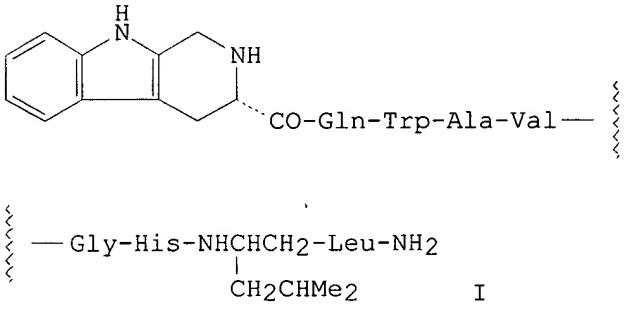
L7 ANSWER 26 OF 27 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1992:15459 HCAPLUS
DOCUMENT NUMBER: 116:15459
TITLE: Inhibition of growth of HT-29 human colon cancer xenografts in nude mice by treatment with bombesin/gastrin releasing peptide antagonist (RC-3095)
AUTHOR(S): Radulovic, Sinisa; Miller, Glenn; Schally, Andrew V.
CORPORATE SOURCE: Endocr., Polypept., Cancer Inst., Veterans Aff. Med. Cent., New Orleans, LA, 70146, USA
SOURCE: Cancer Res. (1991), 51(21), 6006-9
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Nude mice bearing xenografts of HT-29 human colon cancer cell line were treated for 4 wk with a [D-Trp6] agonist of LH-releasing hormone (LH-RH), somatostatin analog RC-160, and bombesin/gastrin releasing peptide antagonist RC-3095. Slight inhibitory effect of [D-Trp6]-LH-RH microcapsules releasing 25 .mu.g/day on tumor growth was obsd. that could be due to sex steroid deprivation. Microcapsules of RC-160, releasing 50 .mu.g/day, reduced tumor vol. after 21 and 24 days of treatment. RC-3095 at 20 .mu.g/day administered by daily s.c. injections or by continuous infusion using Alzet osmotic minipumps, had the greatest inhibitory effect on tumor growth. Tumor vol., percentage change in tumor vol., and tumor wts. were decreased.

IT **138147-78-1**, RC 3095
RL: PRP (Properties)
(**antitumor** effects of, in colon)

L7 ANSWER 27 OF 27 HCAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER: 1992:15458 HCAPLUS
DOCUMENT NUMBER: 116:15458
TITLE: Inhibitory effect of bombesin/gastrin-releasing peptide antagonist RC-3095 and high dose of somatostatin analogue RC-160 on nitrosamine-induced pancreatic cancers in hamsters
AUTHOR(S): Szepeshazi, Karoly; Schally, Andrew V.; Cai, Ren Zhi; Radulovic, Sinisa; Milovanovic, Slobodan; Szoke, Balasz
CORPORATE SOURCE: Med. Sch., Tulane Univ., New Orleans, LA, 70112, USA
SOURCE: Cancer Res. (1991), 51(21), 5980-6
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Female Syrian golden hamsters with N-nitrosobis(2-oxopropyl)amine-induced pancreatic cancers were treated for 2 mo with the bombesin receptor antagonist RC-3095 (I) administered s.c. with osmotic minipumps releasing 20 .mu.g/day of the agent. The results were compared to those obtained by treatment with the somatostatin analog RC-160 (35 and 150 .mu.g/day), [D-Trp6]LH-releasing hormone (25 .mu.g/day), and the acetylated somatostatin analog RC-160-II (30 .mu.g/day). All peptide analogs showed tumor inhibition by at least one of the measured parameters. RC-3095 and the high dose of RC-160 had the greatest inhibitory effect on pancreatic cancers. A decrease in the no. of animals with tumors, reduced pancreatic wt., 87-89% inhibition of tumorous pancreas wt., and a diminution in the no. of tumor nodules and argyrophilic nucleolar organizer region count in tumor cell nuclei were obsd. Receptors for bombesin were detected in membranes of N-nitrosobis(2-oxopropyl)amine-induced pancreatic tumors and these receptors were not down-regulated after treatment with the bombesin antagonist. In hamsters treated with bombesin antagonists, tumor inhibition might be explained by a decrease in the binding capacity of epidermal growth factor receptors in pancreatic cancers. RC-160-II had a similar inhibitory effect on the tumors as RC-160. The increase in the

dose of RC-160 improved the therapeutic response. This finding should be taken into account in clin. use of this somatostatin analog. RC-3095 might be considered as a possible agent for the therapy of human exocrine pancreatic cancer.

IT **138147-78-1**
RL: PRP (Properties)
(**antitumor** effects of, in pancreas **cancer**)

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L8 ANSWER 1 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **166774-43-2** REGISTRY
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CN 2-7-Litorin (peptide), N2-[(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-3-yl)carbonyl]-7-[N-[1-[(4-carboxy-3-thiazolidinyl)methyl]-3-methylbutyl]-L-histidinamide]-, [2(R),7[R-(R*,S*)]]-
OTHER NAMES:
CN RC 3910-II
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MF C54 H72 N14 O10 S
SR CA

LC STN Files: CA, CAPLUS, TOXLIT

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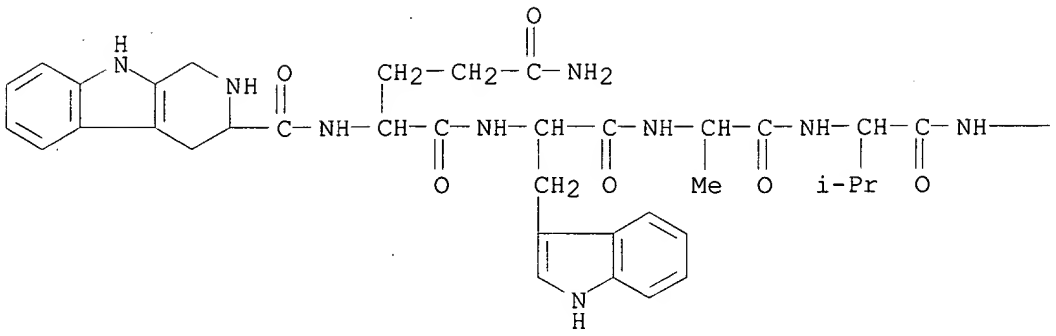

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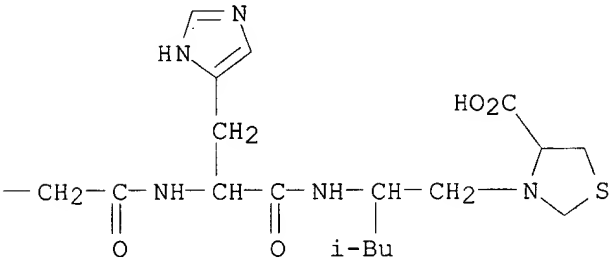

3 REFERENCES IN FILE CA (1967 TO DATE)
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REFERENCE 1: 125:237839

REFERENCE 2: 124:194457

REFERENCE 3: 123:131996

L8 ANSWER 2 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **163878-62-4** REGISTRY
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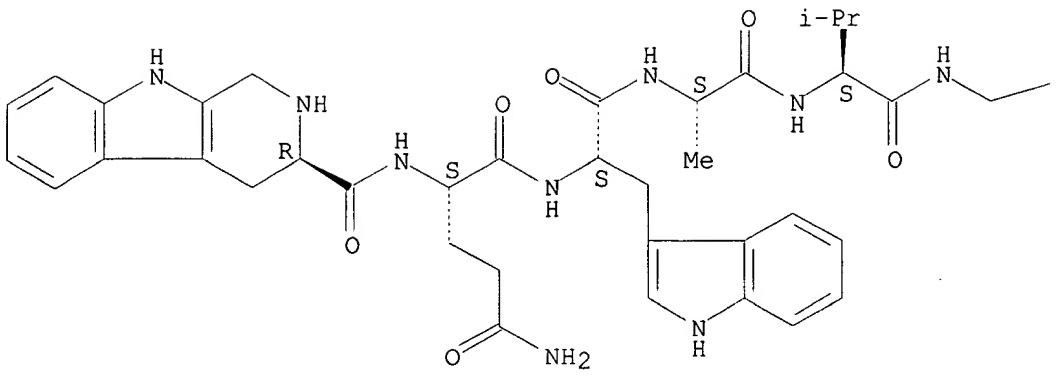
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C68 H86 N14 O11 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

PAGE 1-A



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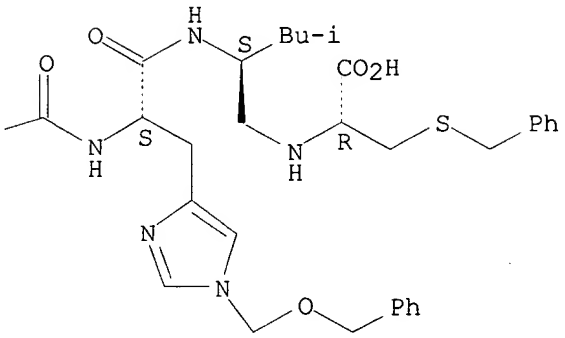

1 REFERENCES IN FILE CA (1967 TO DATE)
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1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 123:9930

L8 ANSWER 3 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **163878-60-2** REGISTRY
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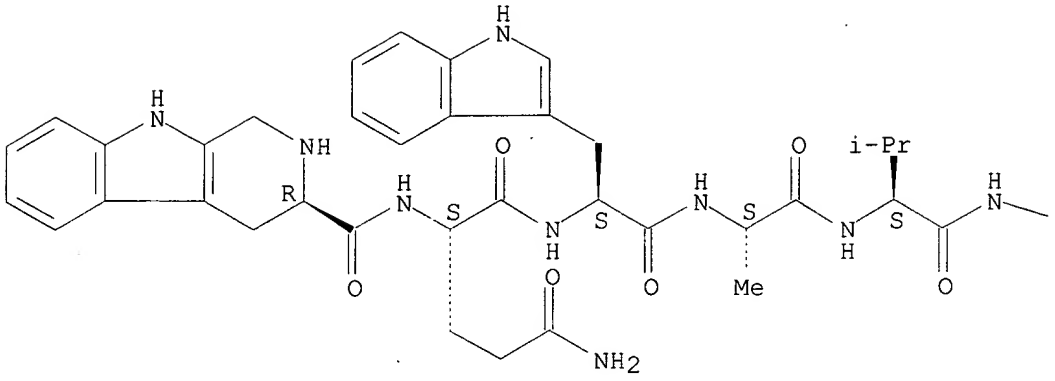
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C56 H77 N15 O9 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

PAGE 1-A



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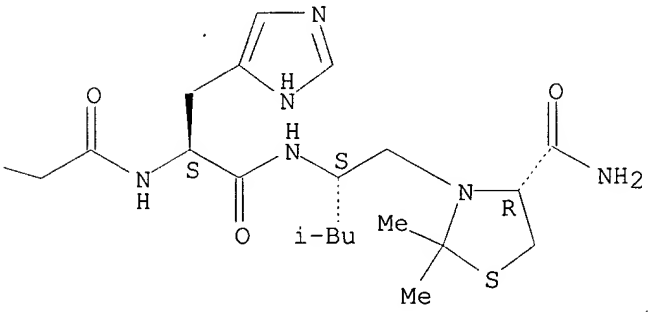

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REFERENCE 1: 123:9930

L8 ANSWER 4 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **163878-59-9** REGISTRY
CN 4-9-Ranatensin, N2-[(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-3-yl)carbonyl]-9-[N-[1-[[4-(aminocarbonyl)-3-thiazolidinyl]methyl]-3-methylbutyl]-L-histidinamide]-, [4(R),9[R-(R*,S*)]]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C54 H73 N15 O9 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

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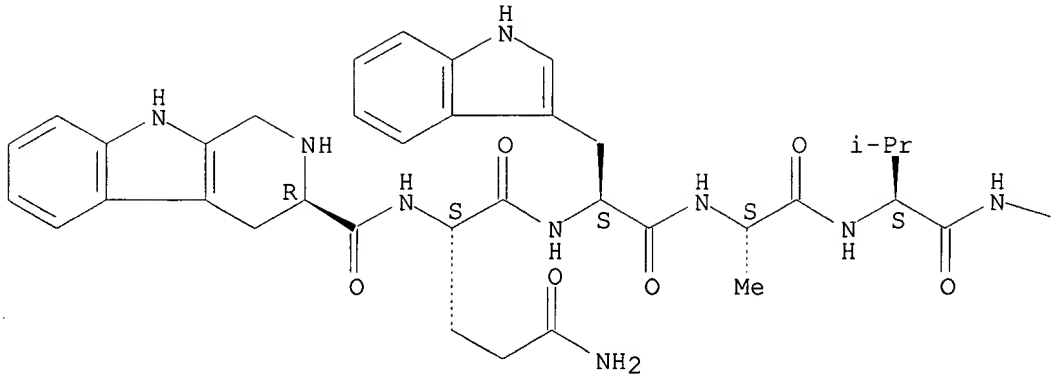

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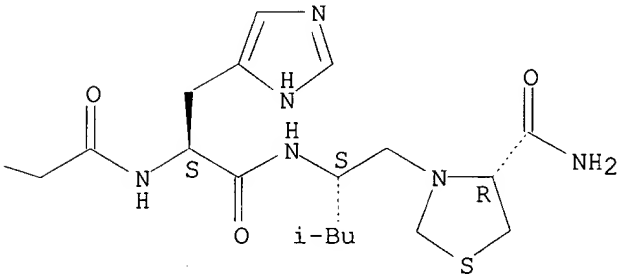

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REFERENCE 1: 123:112728

REFERENCE 2: 123:9930

L8 ANSWER 5 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **163759-38-4** REGISTRY
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FS PROTEIN SEQUENCE; STEREOSEARCH
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SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

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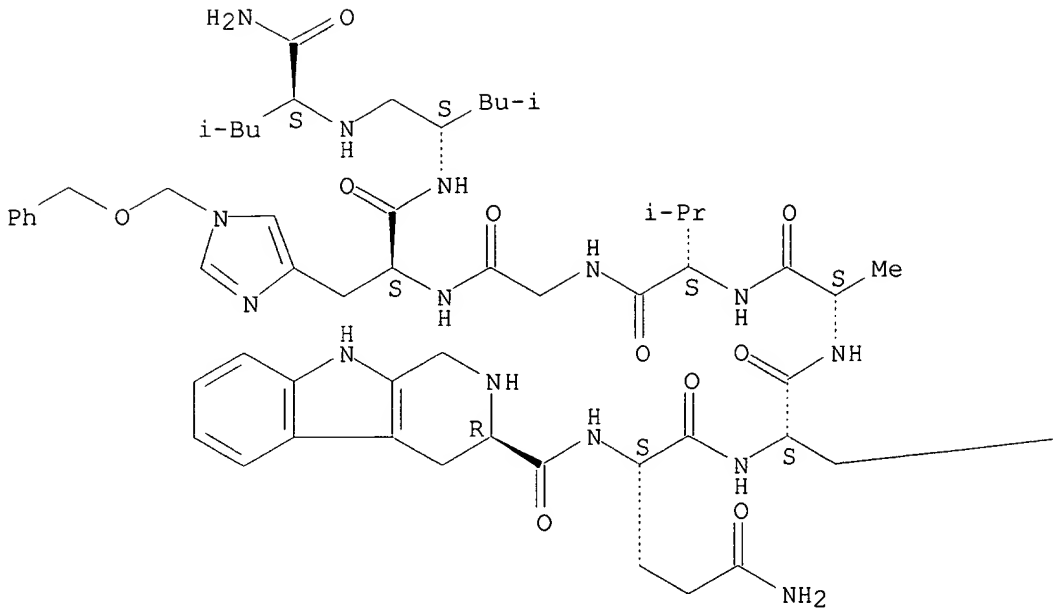

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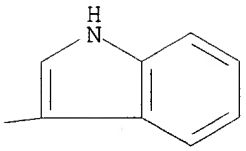

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L8 ANSWER 6 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **163759-36-2** REGISTRY
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FS PROTEIN SEQUENCE; STEREOSEARCH
MF C68 H86 N14 O11 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

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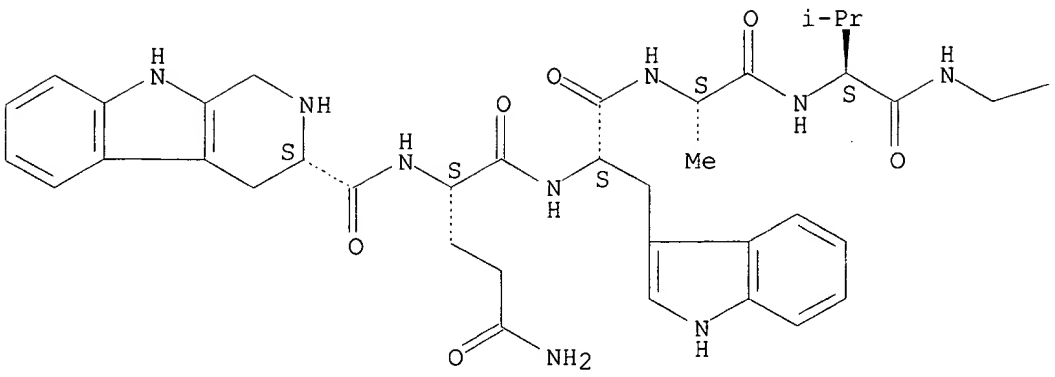

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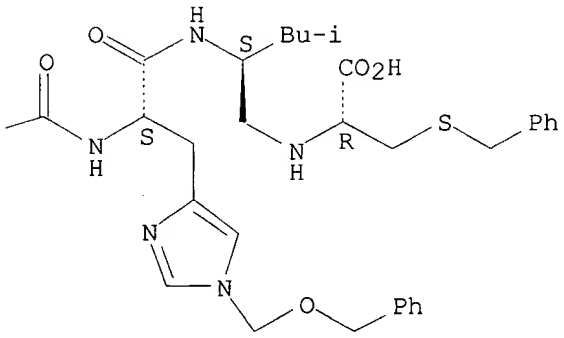

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L8 ANSWER 7 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **163759-34-0** REGISTRY
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LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

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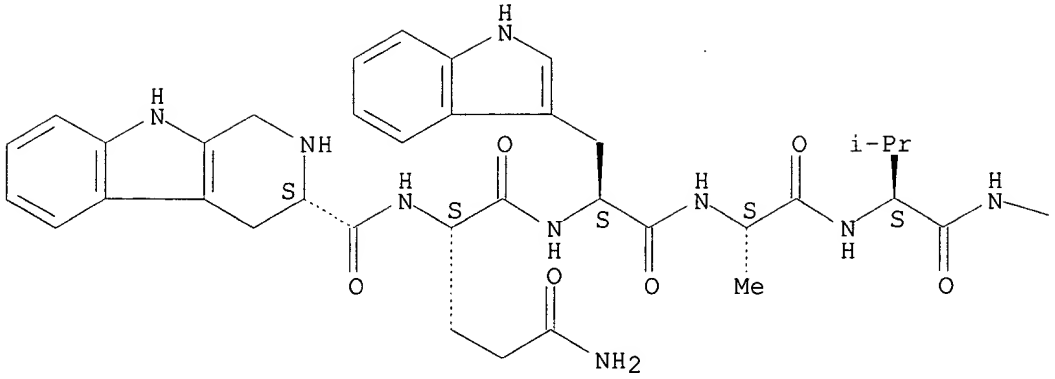

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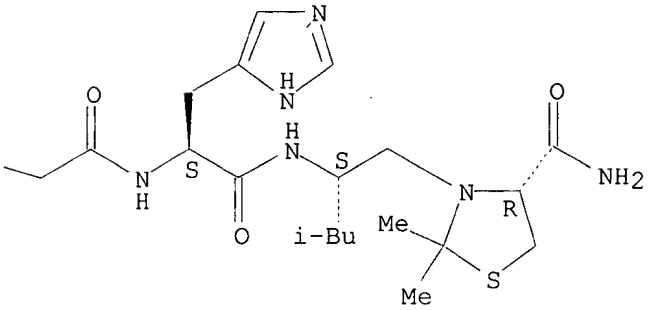

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L8 ANSWER 8 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **163759-26-0** REGISTRY
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MF C54 H73 N15 O9 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

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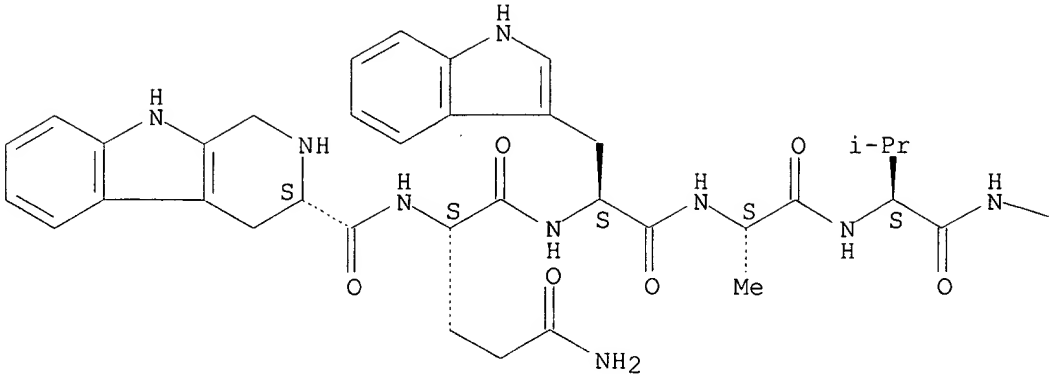

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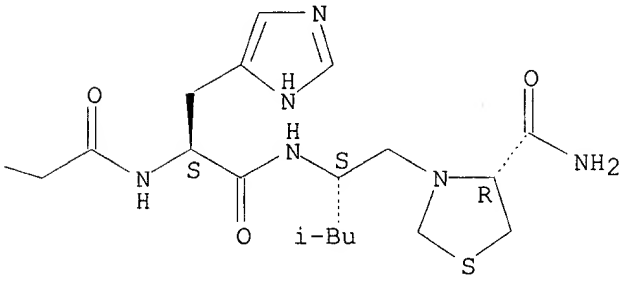

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REFERENCE 2: 123:9930

L8 ANSWER 9 OF 12 REGISTRY COPYRIGHT 2000 ACS
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OTHER CA INDEX NAMES:
CN 1H-Pyrido[3,4-b]indole, L-histidinamide deriv. (9CI)
OTHER NAMES:
CN D 22213
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C56 H79 N15 O9 . C2 H4 O2
SR CA
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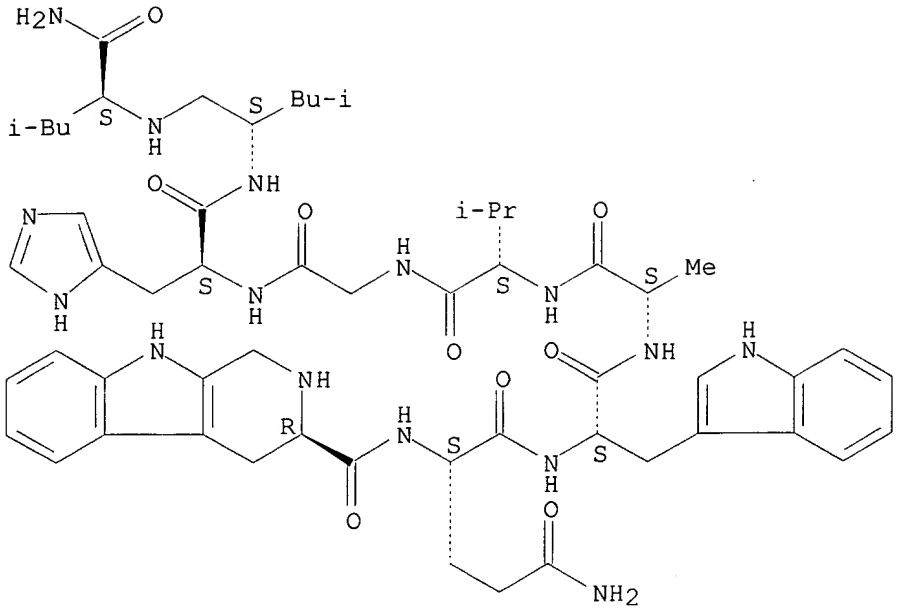
CMF C56 H79 N15 O9

Absolute stereochemistry.



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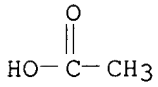

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L8 ANSWER 10 OF 12 REGISTRY COPYRIGHT 2000 ACS
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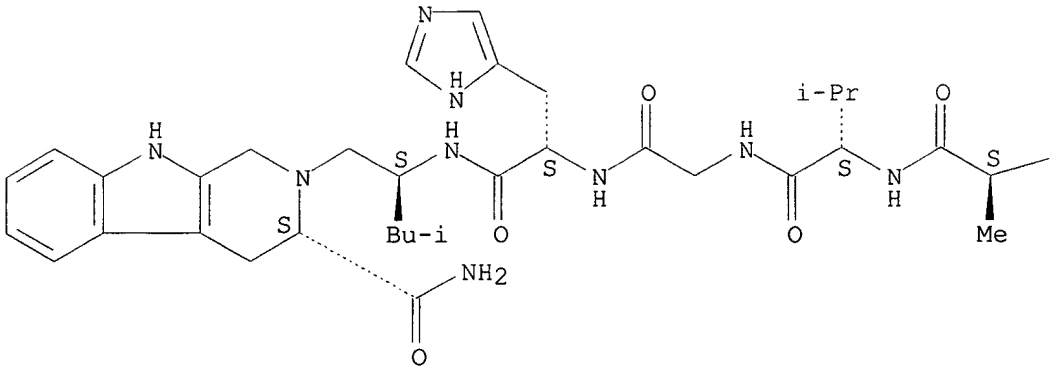
OTHER CA INDEX NAMES:
CN 1H-Pyrido[3,4-b]indole, L-histidinamide deriv.
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C62 H78 N16 O9
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

PAGE 1-A



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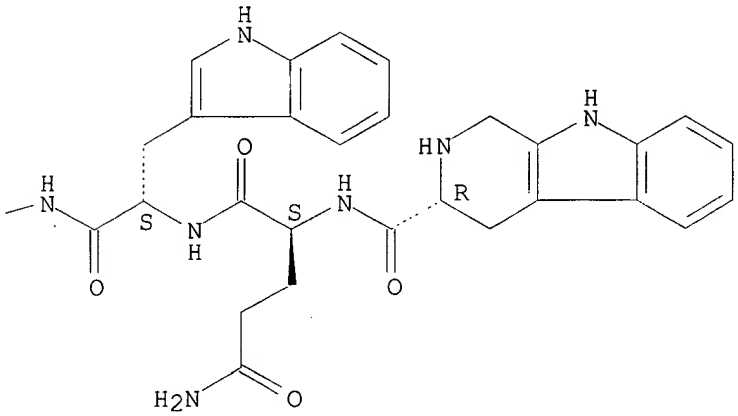

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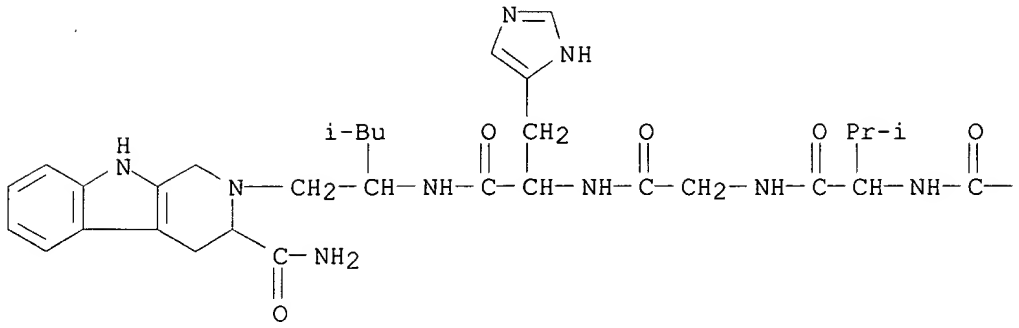
REFERENCE 2: 117:192350

L8 ANSWER 11 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **142824-94-0** REGISTRY
CN L-Histidinamide, N2-[(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-3-yl)carbonyl]-L-glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-N-[1-[[3-(aminocarbonyl)-1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl]methyl]-3-methylbutyl]-, [1(S),6[S-(R*,R*)]]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrido[3,4-b]indole, L-histidinamide deriv.
OTHER NAMES:
CN RC 3440
FS PROTEIN SEQUENCE
MF C62 H78 N16 O9
SR CA
LC STN Files: ADISINSIGHT, CA, CANCERLIT, CAPLUS, MEDLINE, TOXLIT, USPATFULL

PAGE 1-A



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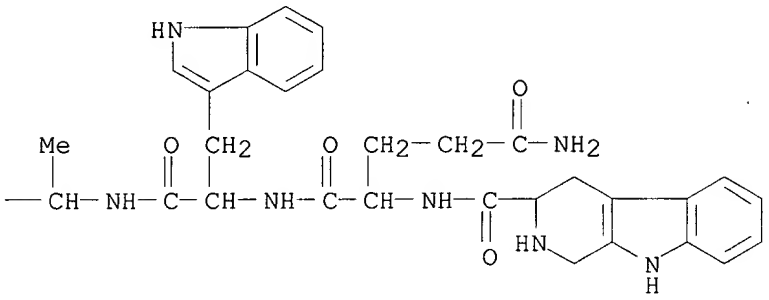


3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

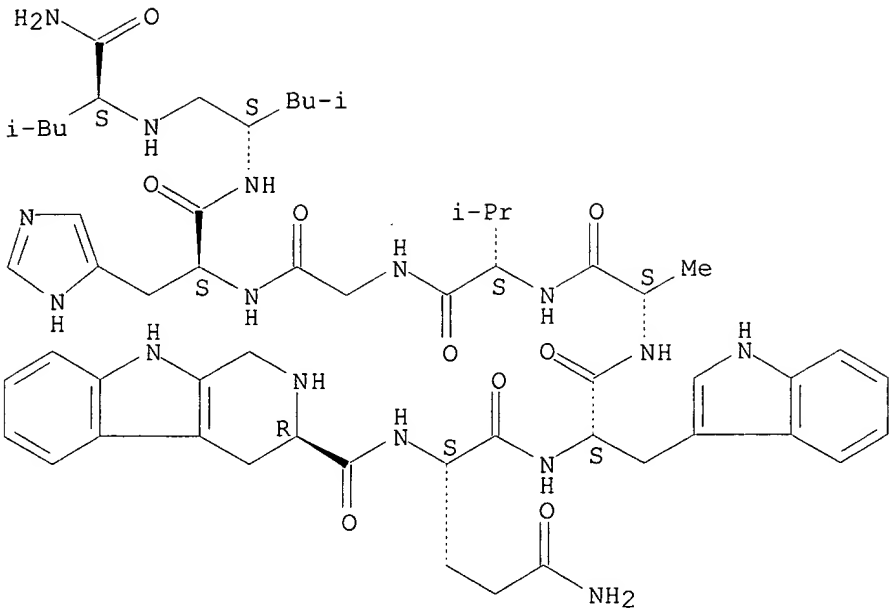
REFERENCE 1: 122:122615

REFERENCE 2: 117:192350

REFERENCE 3: 117:83567

L8 ANSWER 12 OF 12 REGISTRY COPYRIGHT 2000 ACS
RN **138147-78-1** REGISTRY
CN L-Leucinamide, (3R)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carbonyl-L-glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-L-histidyl-L-leucyl-.psi.(CH2-NH)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrido[3,4-b]indole, L-histidinamide deriv.
CN L-Histidinamide, N2-[(2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-3-yl)carbonyl]-L-glutaminyl-L-tryptophyl-L-alanyl-L-valylglycyl-N-[1-[[[1-(aminocarbonyl)-3-methylbutyl]amino]methyl]-3-methylbutyl]-, [1(R),6[S-(R*,R*)]]-
OTHER NAMES:
CN RC 3095
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C56 H79 N15 O9
CI COM
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, CA, CANCERLIT, CAPLUS, CIN, DRUGNL, DRUGUPDATES, EMBASE, MEDLINE, PROMT, TOXLINE, TOXLIT, USPATFULL

Absolute stereochemistry.



40 REFERENCES IN FILE CA (1967 TO DATE)
40 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:194602

REFERENCE 2: 130:60697

REFERENCE 3: 129:144603

REFERENCE 4: 127:314475

REFERENCE 5: 126:246412

REFERENCE 6: 125:237839

REFERENCE 7: 124:283275

REFERENCE 8: 124:194457

REFERENCE 9: 124:105565

REFERENCE 10: 124:76961

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 13:32:01 ON 05 FEB 2000
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1967 - 5 Feb 2000 VOL 132 ISS 7
FILE LAST UPDATED: 4 Feb 2000 (20000204/ED)

This file contains CAS Registry Numbers for easy and accurate

substance identification.

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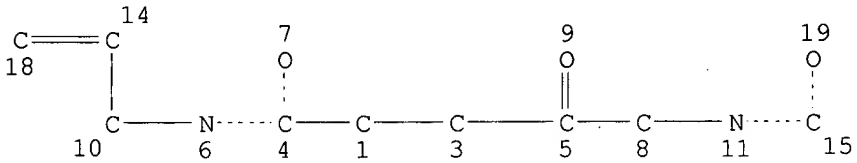
L33 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 14

STEREO ATTRIBUTES: NONE
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L36 6 SEA FILE=HCAPLUS ABB=ON PLU=ON L35

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L36 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:723052 HCAPLUS
DOCUMENT NUMBER: 131:337357
TITLE: Preparation of peptides as antipicornaviral agents
INVENTOR(S): Dragovich, Peter Scott; Marakovits, Joseph Timothy; Prins, Thomas Jay; Tikhe, Jayashree Girish; Webber, Stephen Evan; Zhou, Ru; Johnson, Theodore O.
PATENT ASSIGNEE(S): Agouron Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9957135	A1	19991111	WO 1999-US260	19990105

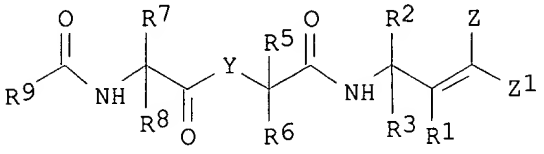
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,

FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1998-83828 19980430
US 1998-98358 19980828

OTHER SOURCE(S): MARPAT 131:337357

GI



I

AB Peptido and peptido-mimetic compds. I (Y = O, substituted N or C; R1 = H, F, alkyl, OH, SH, alkoxy; R2, R3 = independently H, CH2Ch2CONH2, heterocycle; R5, R6 = H, F, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl; R7, R8 = independently H, alkyl, cycloalkyl, heterocycloalkyl, aryl,, heteroaryl, OH, alkoxy, alkylthio, alkylamine, alkoxyamine; R9 = 5-membered heterocycle; Z, Z1 = independently H, F, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, acyl, ester, amide, sulfone) were prepd. and advantageously inhibit or block the biol. activity of the picornaviral 3C protease. These compds., as well as pharmaceutical compns. contg. these compds., are useful for treating patients or hosts infected with one or more picorna-viruses, such as RVP. Thus, ethyl-3-{Cbz-L-Leu-L-Phe-L-((R)-Pyrrol-Ala)}-E-propenoate was prepd. as antipicornaviral agent and protease inhibitor (Kobs/I = 18000 M-1 x sec-1).

IT **214286-28-9P**
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of peptides as antipicornaviral agents and protease inhibitors)

IT **223526-17-8P 223537-30-2P 249736-49-0P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of peptides as antipicornaviral agents and protease inhibitors)

IT **214286-66-5P 223526-69-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of peptides as antipicornaviral agents and protease inhibitors)

L36 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:684462 HCAPLUS
DOCUMENT NUMBER: 132:136
TITLE: Structure-assisted design of mechanism-based irreversible inhibitors of human rhinovirus 3C protease with potent antiviral activity against multiple rhinovirus serotypes
AUTHOR(S): Matthews, D. A.; Dragovich, P. S.; Webber, S. E.; Fuhrman, S. A.; Patick, A. K.; Zalman, L. S.; Hendrickson, T. F.; Love, R. A.; Prins, T. J.; Marakovits, J. T.; Zhou, R.; Tikhe, J.; Ford, C. E.; Meador, J. W.; Ferre, R. A.; Brown, E. L.; Binford, S. L.; Brothers, M. A.; Delisle, D. M.; Worland, S. T.
CORPORATE SOURCE: Agouron Pharmaceuticals, Inc., San Diego, CA, 92121, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1999), 96(20), 11000-11007
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Human rhinoviruses, the most important etiol. agents of the common cold,

are messenger-active single-stranded monocistronic RNA viruses that have evolved a highly complex cascade of proteolytic processing events to control viral gene expression and replication. Most maturation cleavages within the precursor polyprotein are mediated by rhinovirus 3C protease (or its immediate precursor, 3CD), a cysteine protease with a trypsin-like polypeptide fold. High-resoln. crystal structures of the enzyme from three viral serotypes have been used for the design and elaboration of 3C protease inhibitors representing different structural and chem. classes. Inhibitors having .alpha.,.beta.-unsatd. carbonyl groups combined with peptidyl-binding elements specific for 3C protease undergo a Michael reaction mediated by nucleophilic addn. of the enzyme's catalytic Cys-147, resulting in covalent-bond formation and irreversible inactivation of the viral protease. Direct inhibition of 3C proteolytic activity in virally infected cells treated with these compds. can be inferred from dose-dependent accumulations of viral precursor polyproteins as detd. by SDS/PAGE anal. of radiolabeled proteins. Cocrystal-structure-assisted optimization of 3C-protease-directed Michael acceptors has yielded mols. having extremely rapid in vitro inactivation of the viral protease, potent antiviral activity against multiple rhinovirus serotypes and low cellular toxicity. Recently, one compd. in this series, AG7088, has entered clin. trials.

IT **223537-30-2**, AG7088
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(structure-assisted design of irreversible inhibitors of human rhinovirus 3C protease with antiviral activity against multiple rhinovirus serotypes)

L36 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:666921 HCAPLUS
DOCUMENT NUMBER: 131:346180
TITLE: In vitro antiviral activity of AG7088, a potent inhibitor of human rhinovirus 3C protease
AUTHOR(S): Patick, A. K.; Binford, S. L.; Brothers, M. A.; Jackson, R. L.; Ford, C. E.; Diem, M. D.; Maldonado, F.; Dragovich, P. S.; Zhou, R.; Prins, T. J.; Fuhrman, S. A.; Meador, J. W.; Zalman, L. S.; Matthews, D. A.; Worland, S. T.
CORPORATE SOURCE: Agouron Pharmaceuticals, San Diego, CA, 92121, USA
SOURCE: Antimicrob. Agents Chemother. (1999), 43(10), 2444-2450
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB AG-7088 is a potent, irreversible inhibitor of human rhinovirus (HRV) 3C protease (inactivation rate const. kobs/[I] = 1,470,000.+-.440,000 M-1 s-1 for HRV 14) that was discovered by protein structure-based drug design methodologies. In H1-HeLa and MRC-5 cell protection assays, AG-7088 inhibited the replication of all HRV serotypes (48 of 48) tested with a mean 50% EC50 of 0.023 .mu.M (range 0.003-0.081 .mu.M) and a mean EC90 of 0.082 .mu.M (range 0.018-0.261 .mu.M), as well as that of related picornaviruses including coxsackieviruses A21 and B3, enterovirus 70, and echovirus 11. No decreases in the antiviral activity of AG-7088 were obsd. when assays were performed in the presence of .alpha.1-acid glycoprotein or mucin proteins found in nasal secretions. The 50% cytotoxic concn. of AG-7088 was >1000 .mu.M, yielding a therapeutic index of >12,346 to >333,333. In a single-cycle, time-of-addn. assay, AG-7088 had antiviral activity when added up to 6 h after infection. A compd. targeting viral attachment and/or uncoating (WIN-51711) was effective only when added at the initiation of virus infection. Direct inhibition of 3C proteolytic activity in infected cells treated with AG-7088 was demonstrated by SDS-polyacrylamide gel electrophoresis anal. of radiolabeled proteins, which showed a dose-dependent accumulation of viral precursor polyproteins and a decrease of processed protein products. The

broad spectrum of antiviral activity of AG-7088, combined with its efficacy even when added late in the virus life cycle, highlights the advantages of 3C protease as a target and suggests that AG7088 is a promising clin. candidate.

IT **223537-30-2**, Ag 7088
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(AG-7088 in vitro antiviral activity as potent inhibitor of human rhinovirus 3C protease)

L36 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:183127 HCAPLUS
DOCUMENT NUMBER: 130:312063
TITLE: Structure-Based Design, Synthesis, and Biological Evaluation of Irreversible Human Rhinovirus 3C Protease Inhibitors. 4. Incorporation of P1 Lactam Moieties as L-Glutamine Replacements
AUTHOR(S): Dragovich, Peter S.; Prins, Thomas J.; Zhou, Ru; Webber, Stephen E.; Marakovits, Joseph T.; Fuhrman, Shella A.; Patick, Amy K.; Matthews, David A.; Lee, Caroline A.; Ford, Clifford E.; Burke, Benjamin J.; Rejto, Paul A.; Hendrickson, Thomas F.; Tuntland, Tove; Brown, Edward L.; Meador, James W., III; Ferre, Rose Ann; Harr, James E. V.; Kosa, Maha B.; Worland, Stephen T.
CORPORATE SOURCE: Agouron Pharmaceuticals Inc., San Diego, CA, 92121, USA
SOURCE: J. Med. Chem. (1999), 42(7), 1213-1224
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
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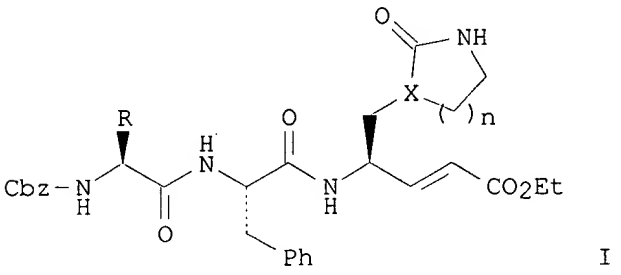

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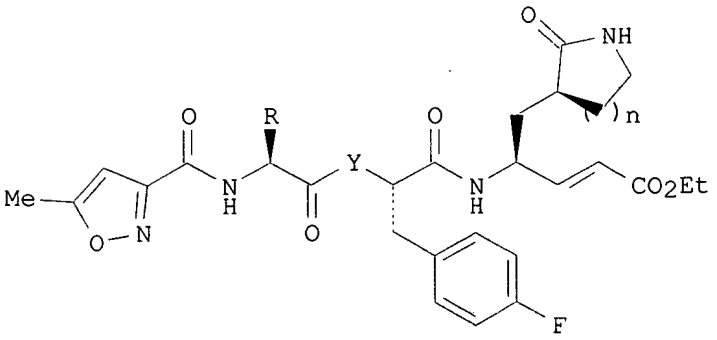


II

AB The structure-based design, chem. synthesis, and biol. evaluation of various human rhinovirus (HRV) 3C protease (3CP) inhibitors, e.g. I [R =

CH2CHMe2, CHMe2; X = (S)-CH, (R)-CH, N; n = 1, 2] and II (R = CHMe2, CMe3; Y = NH, CH2) which incorporate P1 lactam moieties in lieu of an L-glutamine residue are described. These compds. are comprised of a tripeptidyl or peptidomimetic binding determinant and an Et propenoate Michael acceptor moiety which forms an irreversible covalent adduct with the active site cysteine residue of the 3C enzyme. The P1-lactam-contg. inhibitors display significantly increased 3CP inhibition activity along with improved antirhinoviral properties relative to corresponding L-glutamine-derived mols. In addn., several lactam-contg. compds. exhibit excellent selectivity for HRV 3CP over several other serine and cysteine proteases and are not appreciably degraded by a variety of biol. agents. Lactam II (R = CHMe2, Y = CH2, n = 1) (AG7088) was one of the most potent inhibitors (mean antirhinoviral EC90 .apprxeq. 0.10 .mu.M, n = 46 serotypes), and is shown to warrant addnl. preclin. development to explore its potential for use as an antirhinoviral agent.

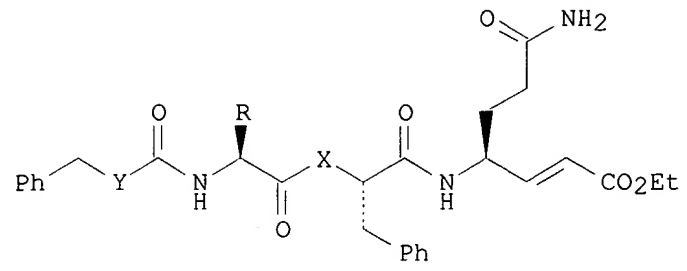
IT **214286-28-9P 223526-17-8P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and human rhinovirus 3C protease inhibitory structure-activity studies of lactam-contg. peptidomimetics)

IT **223526-69-0P 223526-71-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and human rhinovirus 3C protease inhibitory structure-activity studies of lactam-contg. peptidomimetics)

IT **223537-30-2P**, AG 7088
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn., enzymic stability, and human rhinovirus 3C protease inhibitory activity of lactam-contg. peptidomimetics)

L36 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER:	1999:183126 HCAPLUS
DOCUMENT NUMBER:	130:312062
TITLE:	Structure-Based Design, Synthesis, and Biological Evaluation of Irreversible Human Rhinovirus 3C Protease Inhibitors. 3. Structure-Activity Studies of Ketomethylene-Containing Peptidomimetics
AUTHOR(S):	Dragovich, Peter S.; Prins, Thomas J.; Zhou, Ru; Fuhrman, Shella A.; Patick, Amy K.; Matthews, David A.; Ford, Clifford E.; Meador, James W., III; Ferre, Rose Ann; Worland, Stephen T.
CORPORATE SOURCE:	Agouron Pharmaceuticals Inc., San Diego, CA, 92121, USA
SOURCE:	J. Med. Chem. (1999), 42(7), 1203-1212 CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER:	American Chemical Society
DOCUMENT TYPE:	Journal
LANGUAGE:	English
GI	



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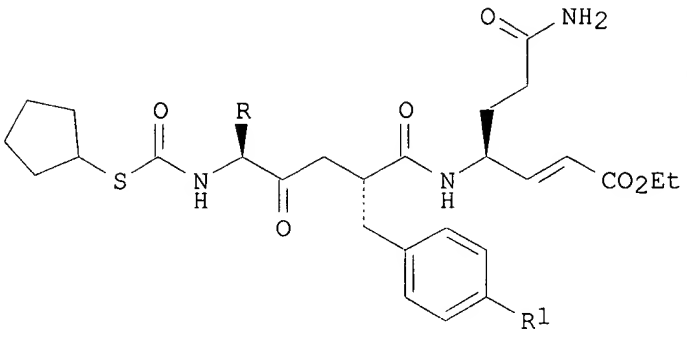

II

AB The structure-based design, chem. synthesis, and biol. evaluation of various ketomethylene-contg. human rhinovirus (HRV) 3C protease (3CP) inhibitors, e.g. I (R = CH2CHMe2, CHMe2; X = NH, CH2; Y = O, S) and II (R = CH2CHMe2, CHMe2, CH2Ph, CMe3; R1 = H, F, Me, CF3) are described. These compds. are comprised of a peptidomimetic binding determinant and an Et propenoate Michael acceptor moiety which forms an irreversible covalent adduct with the active site cysteine residue of the 3C enzyme. The ketomethylene-contg. inhibitors typically display slightly reduced 3CP inhibition activity relative to the corresponding peptide-derived mols., but they also exhibit significantly improved antiviral properties. Optimization of the ketomethylene-contg. compds. is shown to provide several highly active 3C protease inhibitors which function as potent antirhinoviral agents (EC90 = <1 .mu.M) against multiple virus serotypes in cell culture.

IT **214285-95-7P 214285-99-1P 214286-00-7P**
214286-01-8P 214286-02-9P 214286-05-2P
214286-06-3P 214286-08-5P 214286-10-9P
214286-12-1P 214286-13-2P 214286-15-4P
214286-16-5P 214286-28-9P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and human rhinovirus 3C protease inhibitory structure-activity studies of ketomethylene peptidomimetics)

IT **214286-66-5P 214286-70-1P 214286-82-5P**
214286-83-6P 214286-97-2P 214286-98-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and human rhinovirus 3C protease inhibitory structure-activity studies of ketomethylene peptidomimetics)

L36 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:682224 HCAPLUS
DOCUMENT NUMBER: 129:290442
TITLE: Preparation of alkene-ketomethylene pseudopeptides as picornavirus 3C protease inhibitors
INVENTOR(S): Dragovich, Peter S.; Prins, Thomas J.; Zhou, Ru
PATENT ASSIGNEE(S): Agouron Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 175 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9843950	A1	19981008	WO 1998-US6018	19980326
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RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
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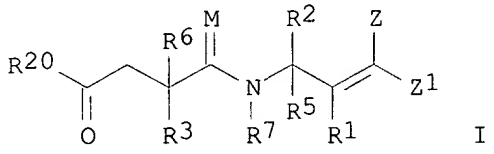
AU 9867788	A1	19981022	AU 1998-67788	19980326
EP 975588	A1	20000202	EP 1998-913173	19980326
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1997-825331 19970328
US 1997-46204 19970512
US 1997-991282 19971216
WO 1998-US6018 19980326

OTHER SOURCE(S): MARPAT 129:290442

GI



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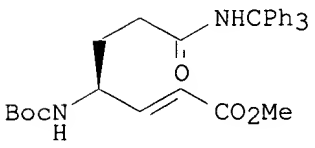

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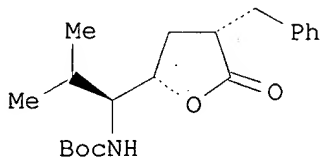

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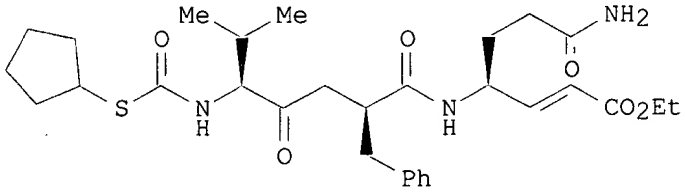

IV

AB Picornaviral 3C protease inhibitors I [M = O, S; R1 = H, F, alkyl, OH, SH, O-alkyl; R2, R5 = H, XY1A1(B1)D1, alkyl different from XY1A1(B1)D1, with the proviso that both R2 and R5 .noteq. H and when R2 or R5 = XY1A1(B1)D1, X = CH or CF and Y1 = CH or CF; R3, R6 = H, F, alkyl; R20 = H, OH, suitable org. moiety; Z, Z1 = H, F, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, etc; XY1 form 3-membered ring with Q1, Q1 = CR10R11, O, X = CH, CF, Y = CH, CF, C-alkyl; R10, R11 = H, halo, alkyl; CR10R11 = cycloalkyl, heterocycloalkyl; X = CH2, CF2, CHF, S; Y1 = O, S, NR12, CR12R14, CO, CS, C(CR13R14); R12 = H, alkyl; R13, R14 = H, F, alkyl; CR13R14 = cycloalkyl, heterocycloalkyl; A1 = C, CH, CF, S, P, Se, N, NR15,

S(O), Se(O), P(OR15), P(NR15R16); R15, R16 = alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl; D1 = moiety contg. electron lone pair capable of forming H bond; B1 = H, F, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, OR17, SR17, NR1718, NR19NR17R18, NR17OR18; R17-R19 = H, any group R15; with provisos], and pharmaceutically acceptable salts thereof and prodrugs thereof, obtainable by chem. synthesis, inhibit or block the biol. activity of picornaviral 3C proteases. These compds., as well as pharmaceutical compns. that contain these compds., are suitable for treating patients or hosts infected with one or more picornaviruses. Several novel methods and intermediates can be used to prep. the novel picornaviral 3C protease inhibitors of the present invention. Thus, olefination of protected glutamine aldehyde Boc-Gln(CPh3)-H (Boc = Me3CO2C), prepd. in 3 steps from Boc-Gln(CPh3)-OH, with tri-Et phosphonoacetate gave (E)-alkene dipeptide isostere II. Deprotection of II and coupling with lactone III [prepd. in 6 steps from isobutyraldehyde, vinylmagnesium bromide, di-Et malonate, (1R,2R)-pseudoephedrine, and benzyl bromide], followed by oxidn., deprotection, thiocarbamoylation with cyclopentyl thiolformate, and detritylation gave desired pseudopeptide IV. IV and 33 related alkene-ketomethylene pseudopeptides were tested for inhibition of rhinovirus protease, antirhinoviral activity, and anticoxsackieviral activity, with IV showing EC50 = 0.022 .mu.M and 0.16 .mu.M for antirhinoviral and anticoxsackieviral activity, resp.

IT **214285-95-7P 214285-96-8P 214285-97-9P**
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214286-14-3P 214286-15-4P 214286-16-5P
214286-17-6P 214286-18-7P 214286-19-8P
214286-20-1P 214286-21-2P 214286-22-3P
214286-23-4P 214286-24-5P 214286-25-6P
214286-26-7P 214286-27-8P 214286-28-9P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of alkene-ketomethylene pseudopeptides as picornavirus 3C protease inhibitors)

IT **214286-32-5P 214286-33-6P 214286-34-7P**
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214286-86-9P 214286-87-0P 214286-88-1P
214286-91-6P 214286-92-7P 214286-97-2P
214286-98-3P 214286-99-4P 214287-06-6P
214287-07-7P 214287-08-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of alkene-ketomethylene pseudopeptides as picornavirus 3C protease inhibitors)

=>

=>

=> fil caold

FILE 'CAOLD' ENTERED AT 13:32:34 ON 05 FEB 2000

FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, and patent assignees are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

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=> s l35

L37 0 L35

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=> fil reg

FILE 'REGISTRY' ENTERED AT 13:33:08 ON 05 FEB 2000
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

STRUCTURE FILE UPDATES: 3 FEB 2000 HIGHEST RN 254763-39-8
DICTIONARY FILE UPDATES: 3 FEB 2000 HIGHEST RN 254763-39-8

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 13, 1999

Please note that search-term pricing does apply when conducting SmartSELECT searches.

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5	RN	223526-17-8	REGISTRY
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L35  ANSWER 1 OF 73  REGISTRY  COPYRIGHT 2000 ACS
RN   249736-49-0  REGISTRY
CN   2-Pentenoic acid, 4-[[2-[(4-fluorophenyl)methyl]-6-methyl-5-[[(5-methyl-3-
     isoxazolyl)carbonyl]amino]-1,4-dioxoheptyl]amino]-5-(2-oxo-3-pyrrolidinyl)-
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FS   3D CONCORD
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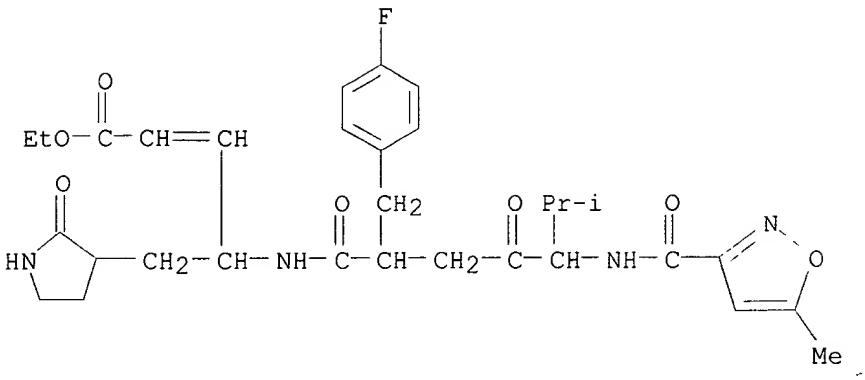
MF C31 H39 F N4 O7
SR CA
LC STN Files: CA, CAPLUS

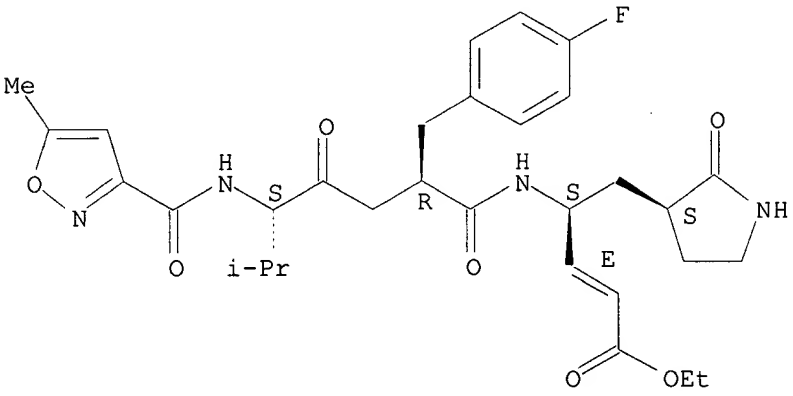


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:337357

L35 ANSWER 2 OF 73 REGISTRY COPYRIGHT 2000 ACS
RN 223537-30-2 REGISTRY
CN 2-Pentenoic acid, 4-[[(2R,5S)-2-[(4-fluorophenyl)methyl]-6-methyl-5-[[(5-methyl-3-isoxazolyl)carbonyl]amino]-1,4-dioxoheptyl]amino]-5-[(3S)-2-oxo-3-pyrrolidinyl]-, ethyl ester, (2E,4S)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN AG 7088
FS STEREOSEARCH
MF C31 H39 F N4 O7
SR CA
LC STN Files: CA, CAPLUS, DRUGNL, DRUGUPDATES, TOXLIT

Absolute stereochemistry.
Double bond geometry as shown.



4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:136

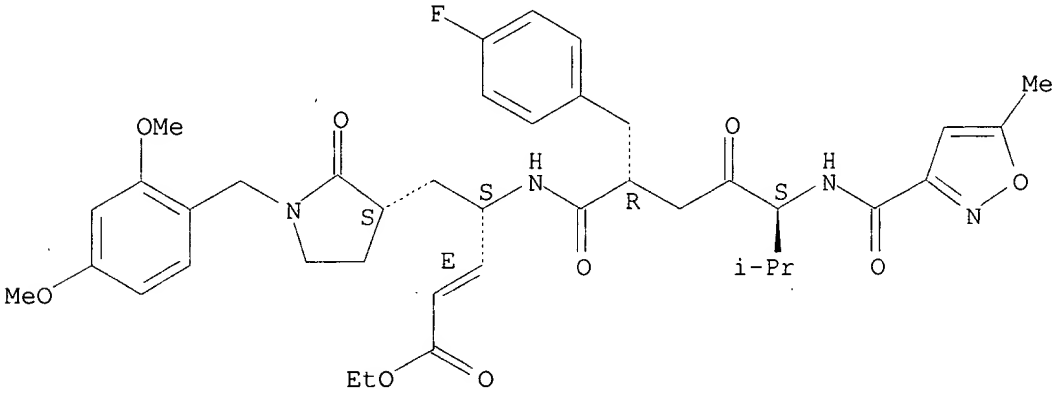
REFERENCE 2: 131:346180

REFERENCE 3: 131:337357

REFERENCE 4: 130:312063

L35 ANSWER 3 OF 73 REGISTRY COPYRIGHT 2000 ACS
RN 223526-71-4 REGISTRY
CN 2-Pentenoic acid, 5-[(3S)-1-[(2,4-dimethoxyphenyl)methyl]-2-oxo-3-pyrrolidinyl]-4-[[(2R,5S)-2-[(4-fluorophenyl)methyl]-6-methyl-5-[[(5-methyl-3-isoxazolyl)carbonyl]amino]-1,4-dioxoheptyl]amino]-, ethyl ester, (2E,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C40 H49 F N4 O9
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.
Double bond geometry as shown.

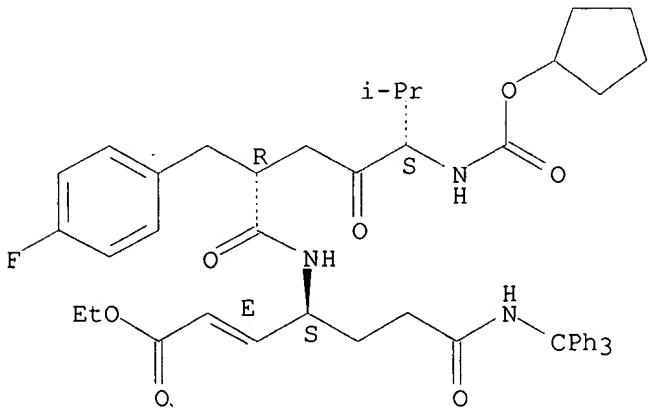


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:312063

L35 ANSWER 6 OF 73 REGISTRY COPYRIGHT 2000 ACS
RN 214287-08-8 REGISTRY
CN 2-Heptenoic acid, 4-[[(2R,5S)-5-[[(cyclopentyloxy)carbonyl]amino]-2-[(4-fluorophenyl)methyl]-6-methyl-1,4-dioxoheptyl]amino]-7-oxo-7-[(triphenylmethyl)amino]-, ethyl ester, (2E,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C49 H56 F N3 O7
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

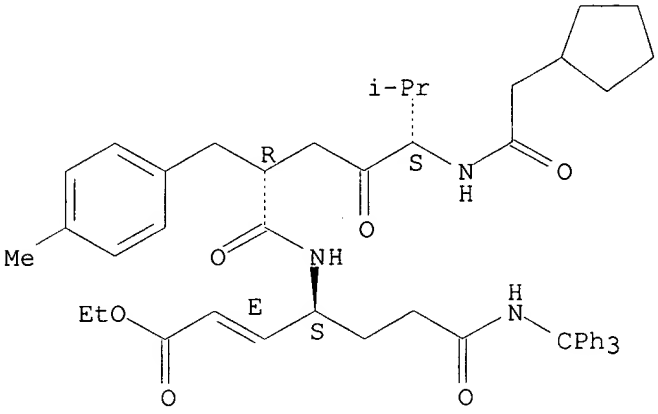


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:290442

L35 ANSWER 9 OF 73 REGISTRY COPYRIGHT 2000 ACS
RN 214286-99-4 REGISTRY
CN 2-Heptenoic acid, 4-[[(2R,5S)-5-[(cyclopentylacetyl)amino]-6-methyl-2-[(4-methylphenyl)methyl]-1,4-dioxoheptyl]amino]-7-oxo-7-[(triphenylmethyl)amino]-, ethyl ester, (2E,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C51 H61 N3 O6
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

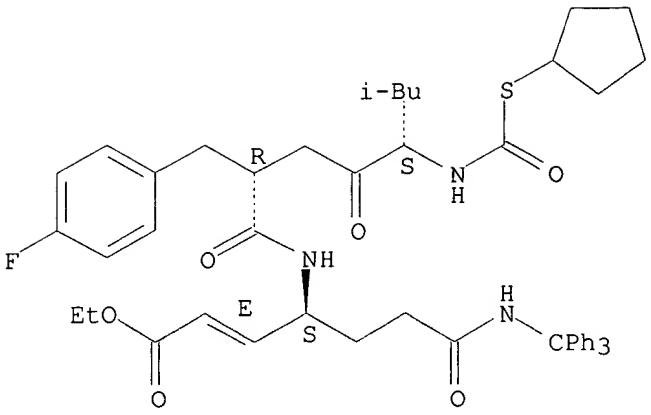


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:290442

L35 ANSWER 15 OF 73 REGISTRY COPYRIGHT 2000 ACS
RN 214286-87-0 REGISTRY
CN 2-Heptenoic acid, 4-[[(2R,5S)-5-[[(cyclopentylthio)carbonyl]amino]-2-[(4-fluorophenyl)methyl]-7-methyl-1,4-dioxooctyl]amino]-7-oxo-7-[(triphenylmethyl)amino]-, ethyl ester, (2E,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C50 H58 F N3 O6 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

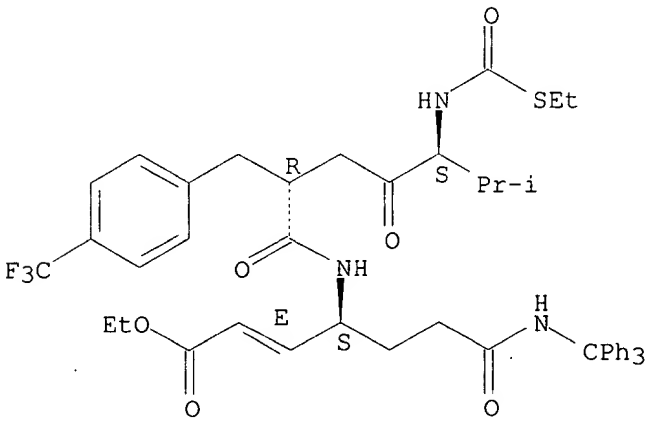


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:290442

L35 ANSWER 20 OF 73 REGISTRY COPYRIGHT 2000 ACS
RN 214286-76-7 REGISTRY
CN 2-Heptenoic acid, 4-[[(2R,5S)-5-[[(ethylthio)carbonyl]amino]-6-methyl-1,4-dioxo-2-[[4-(trifluoromethyl)phenyl]methyl]heptyl]amino]-7-oxo-7-[(triphenylmethyl)amino]-, ethyl ester, (2E,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C47 H52 F3 N3 O6 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.



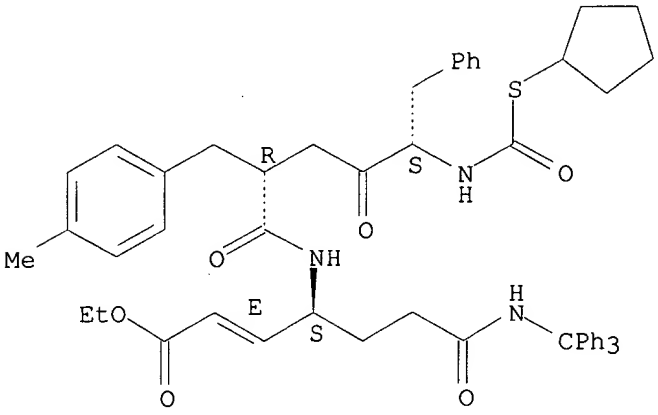
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:290442

L35 ANSWER 25 OF 73 REGISTRY COPYRIGHT 2000 ACS
RN 214286-59-6 REGISTRY
CN 2-Heptenoic acid, 4-[[(2R,5S)-5-[[(cyclopentylthio)carbonyl]amino]-2-[(4-methylphenyl)methyl]-1,4-dioxo-6-phenylhexyl]amino]-7-oxo-7-[(triphenylmethyl)amino]-, ethyl ester, (2E,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C54 H59 N3 O6 S
SR CA

LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

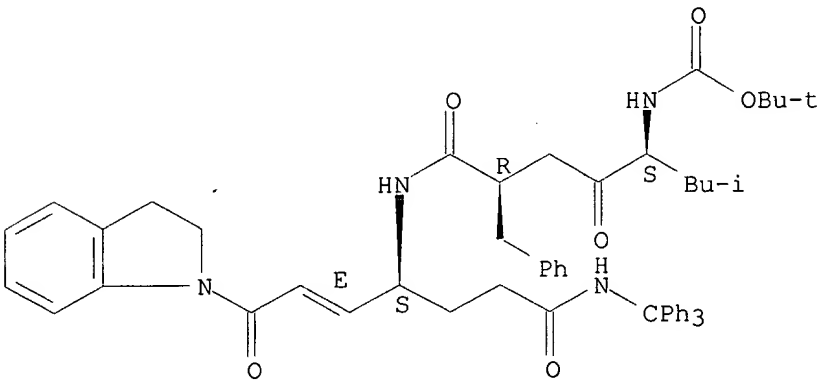


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:290442

L35 ANSWER 30 OF 73 REGISTRY COPYRIGHT 2000 ACS
RN 214286-49-4 REGISTRY
CN Carbamic acid, [(1S,4R)-5-[[(1S,2E)-4-(2,3-dihydro-1H-indol-1-yl)-4-oxo-1-[3-oxo-3-[(triphenylmethyl)amino]propyl]-2-butenyl]amino]-1-(2-methylpropyl)-2,5-dioxo-4-(phenylmethyl)pentyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C55 H62 N4 O6
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.



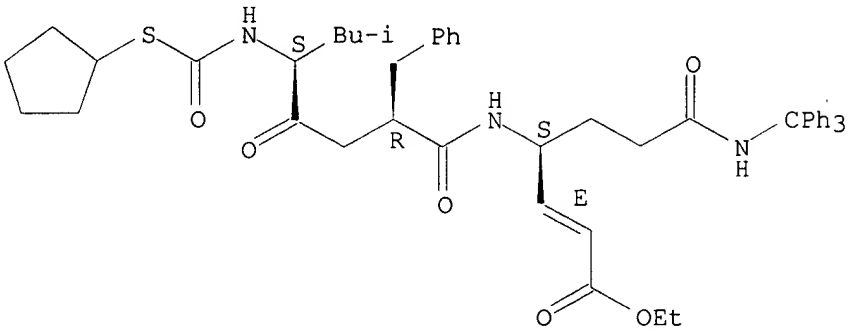
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:290442

L35 ANSWER 35 OF 73 REGISTRY COPYRIGHT 2000 ACS
RN 214286-37-0 REGISTRY
CN 2-Heptenoic acid, 4-[[(2R,5S)-5-[[(cyclopentylthio)carbonyl]amino]-7-methyl-1,4-dioxo-2-(phenylmethyl)octyl]amino]-7-oxo-7-

[(triphenylmethyl)amino]-, ethyl ester, (2E,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C50 H59 N3 O6 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

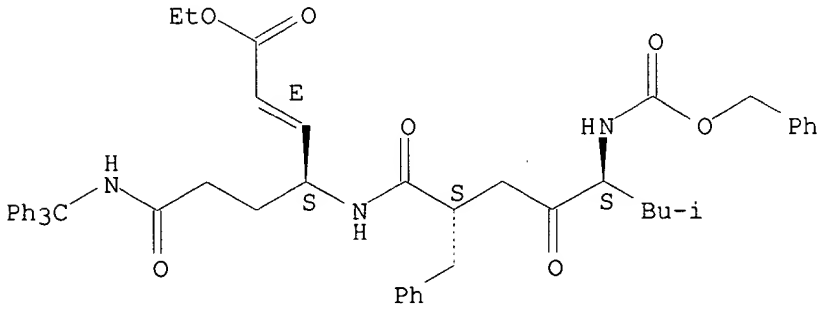


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:290442

L35 ANSWER 40 OF 73 REGISTRY COPYRIGHT 2000 ACS
RN 214286-32-5 REGISTRY
CN 2-Heptenoic acid, 4-[[(2S,5S)-7-methyl-1,4-dioxo-5-[[(phenylmethoxy)carbonyl]amino]-2-(phenylmethyl)octyl]amino]-7-oxo-7-[(triphenylmethyl)amino]-, ethyl ester, (2E,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C52 H57 N3 O7
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.



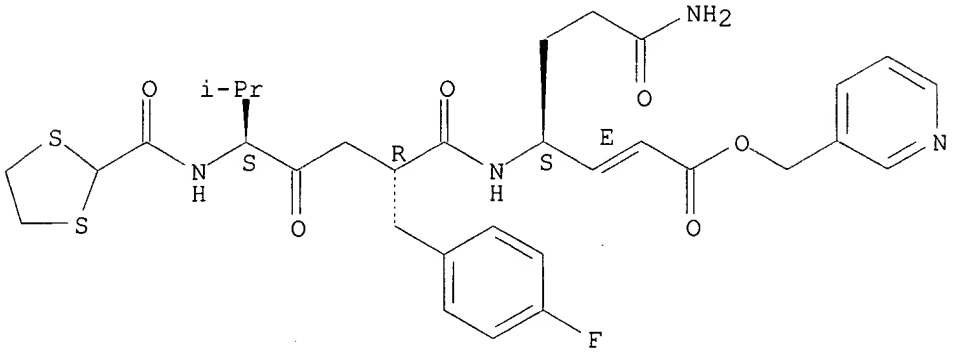
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:290442

L35 ANSWER 45 OF 73 REGISTRY COPYRIGHT 2000 ACS
RN 214286-24-5 REGISTRY
CN 2-Heptenoic acid, 7-amino-4-[[(2R,5S)-5-[(1,3-dithiolan-2-ylcarbonyl)amino]-2-[(4-fluorophenyl)methyl]-6-methyl-1,4-dioxoheptyl]amino]-7-oxo-, 3-pyridinylmethyl ester, (2E,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH

MF C32 H39 F N4 O6 S2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

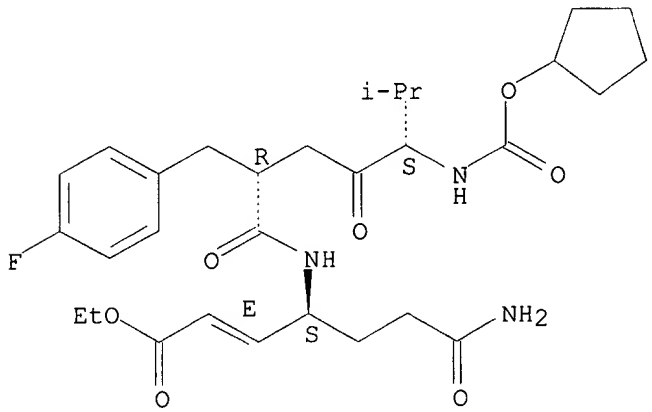


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:290442

L35 ANSWER 50 OF 73 REGISTRY COPYRIGHT 2000 ACS
RN 214286-19-8 REGISTRY
CN 2-Heptenoic acid, 7-amino-4-[[(2R,5S)-5-[[(cyclopentyloxy)carbonyl]amino]-2-[(4-fluorophenyl)methyl]-6-methyl-1,4-dioxoheptyl]amino]-7-oxo-, ethyl ester, (2E,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H42 F N3 O7
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:290442

L35 ANSWER 55 OF 73 REGISTRY COPYRIGHT 2000 ACS
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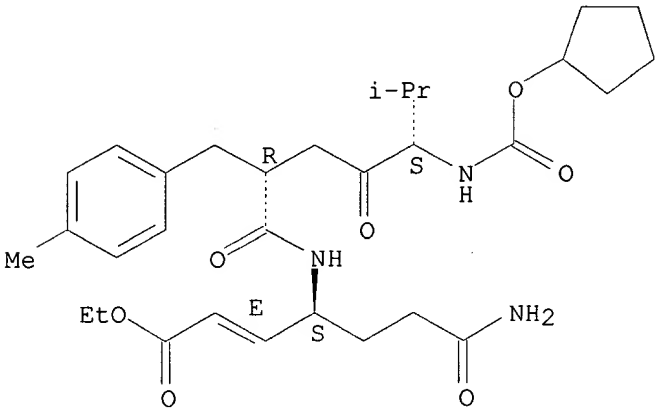
ester, (2E,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H45 N3 O7
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.

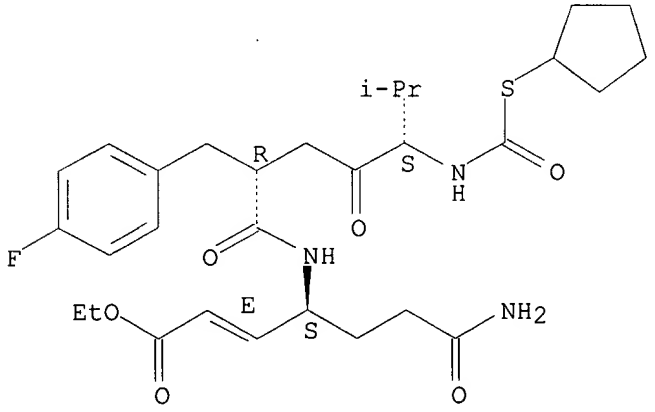


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:290442

L35 ANSWER 60 OF 73 REGISTRY COPYRIGHT 2000 ACS
RN 214286-08-5 REGISTRY
CN 2-Heptenoic acid, 7-amino-4-[[(2R,5S)-5-[[(cyclopentylthio)carbonyl]amino]-2-[(4-fluorophenyl)methyl]-6-methyl-1,4-dioxoheptyl]amino]-7-oxo-, ethyl ester, (2E,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H42 F N3 O6 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.



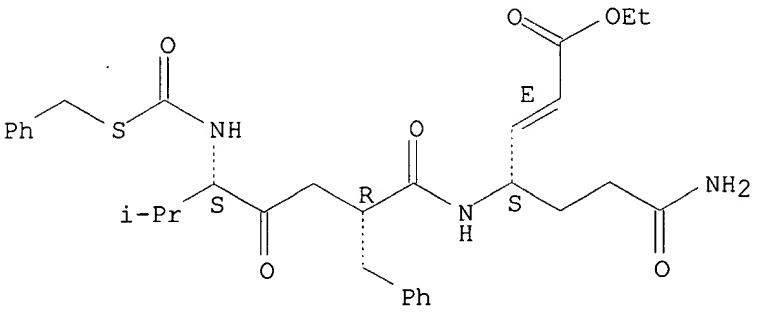
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:312062

REFERENCE 2: 129:290442

L35 ANSWER 69 OF 73 REGISTRY COPYRIGHT 2000 ACS
RN 214285-99-1 REGISTRY
CN 2-Heptenoic acid, 7-amino-4-[[(2R,5S)-6-methyl-1,4-dioxo-2-(phenylmethyl)-5-[[[(phenylmethyl)thio]carbonyl]amino]heptyl]amino]-7-oxo-, ethyl ester, (2E,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C32 H41 N3 O6 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.



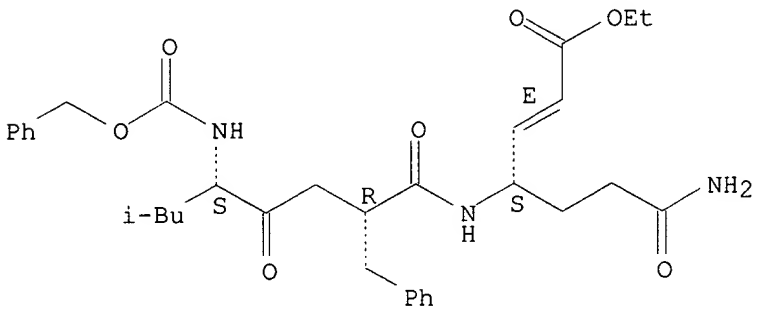
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:312062

REFERENCE 2: 129:290442

L35 ANSWER 73 OF 73 REGISTRY COPYRIGHT 2000 ACS
RN 214285-95-7 REGISTRY
CN 2-Heptenoic acid, 7-amino-4-[[(2R,5S)-7-methyl-1,4-dioxo-5-[[(phenylmethoxy)carbonyl]amino]-2-(phenylmethyl)octyl]amino]-7-oxo-, ethyl ester, (2E,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C33 H43 N3 O7
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:312062

REFERENCE 2: 129:290442

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 11:24:02 ON 07 FEB 2000
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FILE COVERS 1967 - 7 Feb 2000 VOL ISS 7 ISS ISS
FILE LAST UPDATED: 6 Feb 2000 (20000206/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

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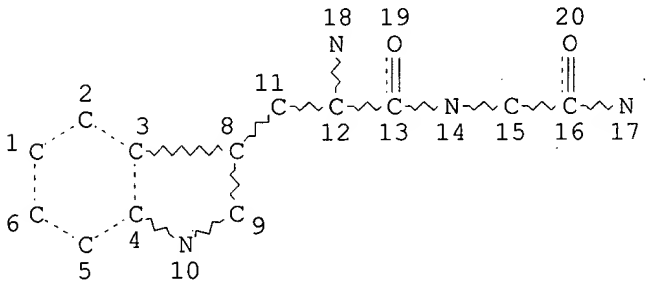
=> d stat que l9

L4 STR



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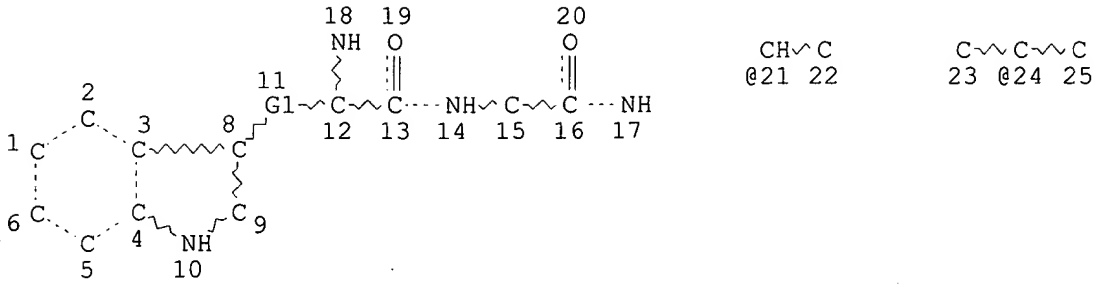
NSPEC IS RC AT 18
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
L6 48289 SEA FILE=REGISTRY SSS FUL L4
L7 STR



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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 24

STEREO ATTRIBUTES: NONE
L8 13 SEA FILE=REGISTRY SUB=L6 SSS FUL L7
L9 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L8

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=> d ibib abs hitrn 19 1-3

L9 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:682285 HCAPLUS
DOCUMENT NUMBER: 129:316555
TITLE: Preparation of peptides as somatostatin agonists
INVENTOR(S): Yang, Lihu; Patchett, Arthur A.; Pasternak, Alexander; Berk, Scott; Chen, Meng Hsin; Johnston, David; Chapman, Kevin; Nargund, Ravi; Tata, James R.; Guo, Liangqin
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; et al.
SOURCE: PCT Int. Appl., 134 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9844922	A1	19981015	WO 1998-US6488	19980402
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9867939	A1	19981030	AU 1998-67939	19980402
PRIORITY APPLN. INFO.:			US 1997-42637	19970404
			US 1997-64378	19971106
			WO 1998-US6488	19980402

OTHER SOURCE(S): MARPAT 129:316555
AB Peptides R8-Q-CR1cW-Z2-CO-CR1R1a-Z1-E-B-GYZ [R1 = alkyl, aryl, arylalkyl,

etc.; R1a = H, alkyl; R1c = H, alkyl, alkoxyalkyl, alkylthioalkyl, etc.; Z1 = O, CH2, NR2a (R2a = H, alkyl, hydroxyalkyl); Z2 = O, CH2, CHR2b, NR2b (R2b = H, alkyl, arylalkyl, etc.; NR2b can be linked to R1c, Q or W to form a ring); W = H, alkyl, arylalkyl, heteroarylalkyl; Q = (un)substituted alkylene or alkylene interrupted by a N, S, or O atom; R8 = (un)substituted amino, guanidino, or ammonio group; E = SO2, C:NNO2, etc.; B = certain divalent aza heterocyclic group; GYX represents an arom. or nonarom. ring structure contg. a ring fusion (G = N, CH, C; Y = CO, SO2, N, etc.; X = N, O, s, etc.)] were prepd. as somatostatin agonists which are potent with high selectivity toward the receptor subtype 2. Thus, N-[[4-(2-oxo-1-benzimidazolinyl)-1-piperidinyl]carbonyl]-D-tryptophanyl-L-lysine Me ester was prepd. by peptide coupling in soln. Title peptides were assayed for receptor binding, inhibition of forskolin-stimulated cAMP accumulation and of growth hormone release.

IT **214784-72-2P 214784-73-3P 214784-74-4P**
214784-75-5P 214784-77-7P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of peptides as somatostatin agonists)

L9 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:626393 HCAPLUS
DOCUMENT NUMBER: 119:226393
TITLE: Synthesis and conformations of somatostatin-related cyclic hexapeptides incorporating specific .alpha.- and .beta.-methylated residues
AUTHOR(S): He, Ya Bo; Huang, Ziwei; Raynor, Karen; Reisine, Terry; Goodman, Murray
CORPORATE SOURCE: Dep. Chem., Univ. California, La Jolla, CA, 92093, USA
SOURCE: J. Am. Chem. Soc. (1993), 115(18), 8066-72
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The cyclic hexapeptide cyclo[Pro6-Phe7-D-Trp8-Lys9-Thr10-Phe11] displays high biol. activities in inhibiting the release of many bioactive mols., including growth hormone, insulin, and glucagon. The superscript nos. refer to the location of the residues in native somatostatin. Conformational studies of this cyclic hexapeptide indicated considerable conformational flexibility in various regions of backbone and side chains. The flexibility prevents the elucidation of the "bioactive conformation" of this mol. when bound to a receptor. To reduce the conformational flexibility, the authors have synthesized one main chain methylated analog contg. .alpha.-MeVal at position 10, cyclo[Pro6-Phe7-D-Trp8-Lys9-(S)-.alpha.-MeVal10-Phe11], and two side chain methylated analogs contg. .beta.-MeTrp and .beta.-MePhe at positions 8 and 11, resp., cyclo[Pro6-Phe7-(2R,3S)-.beta.-MeTrp8-Lys9-Thr10-(2S,3S)-.beta.-MePhe11] and cyclo[Pro6-Phe7-(2S,3R)-.beta.-MeTrp8-Lys9-Thr10(2S,3S)-.beta.-MePhe11]. The effect of main chain and side chain methylations has been studied using 500-MHz two-dimensional 1H-NMR and computer simulations. These main chain and side chain methylated analogs display constrained conformational preferences at the modified backbone and side chains. One of the side chain methylated analogs shows high potency in receptor binding. Conformational studies of these analogs provide valuable information about the main chain and side chain conformation required for receptor interaction. This study clearly demonstrated a novel approach using main chain and side chain methylations in the elucidation of the bioactive conformation of somatostatin analogs. This approach may have important implications in the study of other peptide hormones and neurotransmitters.

IT **150805-42-8P 150805-43-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and deblocking and cyclization of)

IT **150805-40-6DP**, resin-bound **150805-41-7DP**, resin-bound
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and partial deblocking and resin cleavage of)

L9 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1993:60082 HCAPLUS
DOCUMENT NUMBER: 118:60082
TITLE: Main chain and side chain chiral methylated somatostatin analogs: syntheses and conformational analyses
AUTHOR(S): Huang, Ziwei; He, Ya Bo; Raynor, Karen; Tallent, Melanie; Reisine, Terry; Goodman, Murray
CORPORATE SOURCE: Dep. Chem., Univ. California, San Diego, La Jolla, CA, 92093, USA
SOURCE: J. Am. Chem. Soc. (1992), 114(24), 9390-401
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An integrated approach was developed for investigating the bioactive conformations of the main chain and side chains for the somatostatin analog cyclo(Pro6-Phe7-D-Trp8-Lys9-Thr10-Phe11). A series of analogs, e.g. cyclo[Pro-(2S,3R)-.beta.-MePhe-D-Trp-Lys-Thr-Phe] and cyclo[Pro-Phe-(2R,3S)-D-Trp-Lys-Thr-Phe], have been synthesized incorporating .alpha.-methylated and .beta.-methylated residues at positions 7, 8, and 11. These analogs display dramatic differences in in vitro binding affinities for somatostatin receptors. Using 500-MHZ 1H NMR and computer simulations, the effect of main chain and side chain chiral methylations on the overall structure were assessed. The analyses of the changes of side chain topologies and subsequent binding affinities in the .beta.-methylated analogs have provided definitive evidence about the bioactive conformation of the side chains of Phe7, Trp8, and Phe11. The analyses of the .alpha.-methylated analogs have defined a "folded" feature for the peptide backbone. From this study, we have proposed a binding "pocket" for somatostatin analogs which consists of the side chains of Trp8 and Lys9, the peptide backbone, and the side chain of Phe11 in a folded topochem. array. In this folded conformation, the Trp8 side chain assumes the trans rotamer, while the Lys9 side chain assumes the gauche rotamer, thus allowing a close proximity between these two side chains. The Phe11 side chain assumes the trans rotamer. The peptide backbone adopts a .beta. .lambda..lambda.' turn about Trp8-Lys9 and a .beta. VI turn about Phe11-Pro6. The overall structure is folded about Phe7 and Thr10 residues assuming a C7 conformation for their .vphi. and .psi. torsions. This model should have important implications on the future design of peptide or nonpeptide ligands with somatostatin-like activities.
IT **145432-62-8P 145432-64-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and cyclization of)

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=> fil caold

FILE 'CAOLD' ENTERED AT 11:24:28 ON 07 FEB 2000
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FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, and patent assignees are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=>

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=> s 18

L10 0 L8

=>

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=> fil reg

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STRUCTURE FILE UPDATES: 4 FEB 2000 HIGHEST RN 254912-96-4
DICTIONARY FILE UPDATES: 4 FEB 2000 HIGHEST RN 254912-96-4

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 13, 1999

Please note that search-term pricing does apply when conducting SmartSELECT searches.

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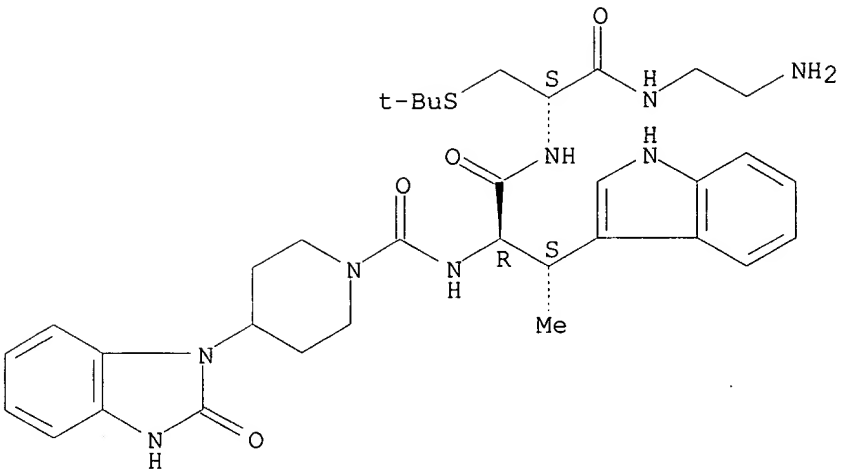
=> d ide can 18 1-13

L8 ANSWER 1 OF 13 REGISTRY COPYRIGHT 2000 ACS
RN 214784-77-7 REGISTRY
CN D-Cysteinamide, N-[[4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]carbonyl]-(.beta.S)-.beta.-methyl-D-tryptophyl-N-(2-aminoethyl)-S-(1,1-dimethylethyl)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C34 H46 N8 O4 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

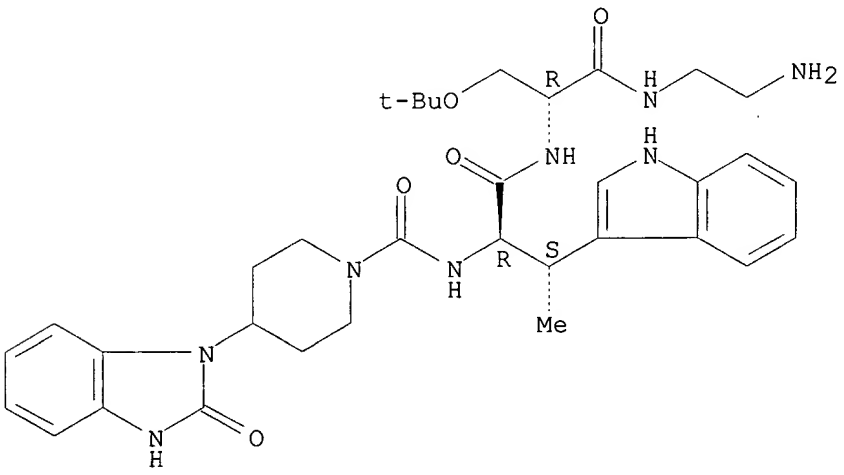


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:316555

L8 ANSWER 2 OF 13 REGISTRY COPYRIGHT 2000 ACS
RN 214784-75-5 REGISTRY
CN D-Serinamide, N-[[4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]carbonyl]-(.beta.S)-.beta.-methyl-D-tryptophyl-N-(2-aminoethyl)-O-(1,1-dimethylethyl)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C34 H46 N8 O5
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



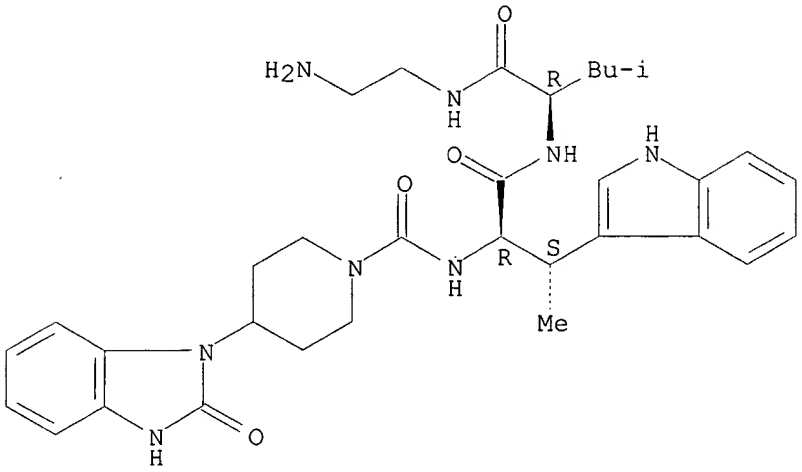
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:316555

L8 ANSWER 3 OF 13 REGISTRY COPYRIGHT 2000 ACS
RN 214784-74-4 REGISTRY
CN D-Leucinamide, N-[[4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]carbonyl]-(.beta.S)-.beta.-methyl-D-tryptophyl-N-(2-aminoethyl)- (9CI) (CA INDEX NAME)

FS STEREOSEARCH
MF C33 H44 N8 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

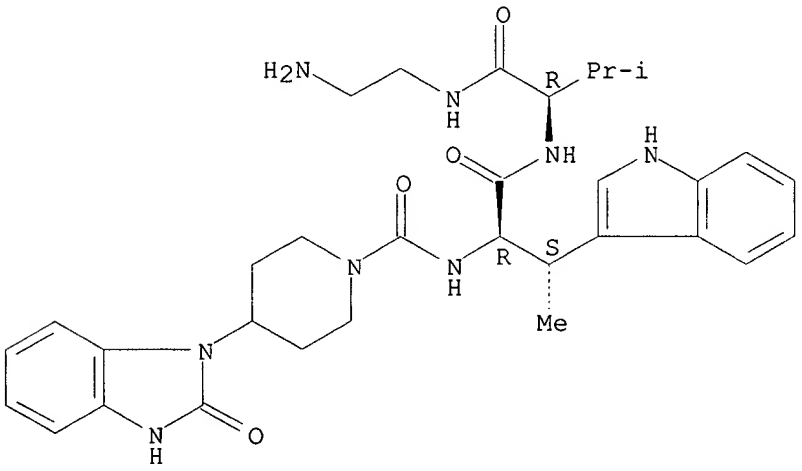


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:316555

L8 ANSWER 4 OF 13 REGISTRY COPYRIGHT 2000 ACS
RN 214784-73-3 REGISTRY
CN D-Valinamide, N-[[4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]carbonyl]-(.beta.S)-.beta.-methyl-D-tryptophyl-N-(2-aminoethyl)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C32 H42 N8 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

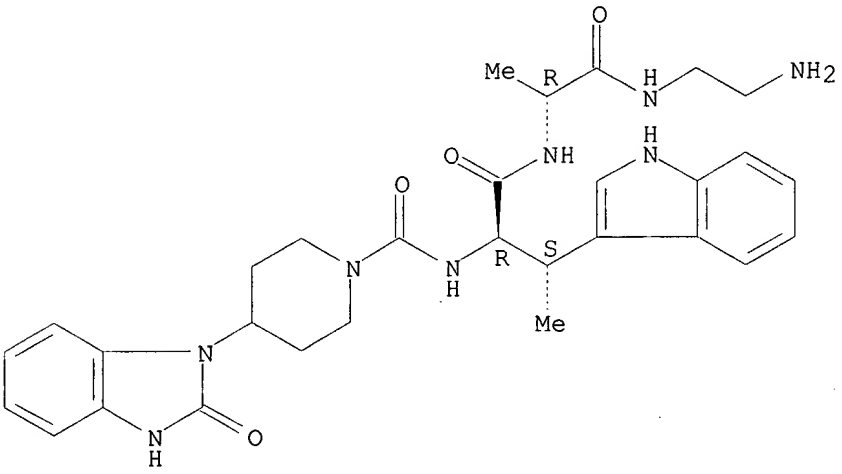


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:316555

L8 ANSWER 5 OF 13 REGISTRY COPYRIGHT 2000 ACS
RN 214784-72-2 REGISTRY
CN D-Alaninamide, N-[[4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]carbonyl]-(.beta.S)-.beta.-methyl-D-tryptophyl-N-(2-aminoethyl)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H38 N8 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



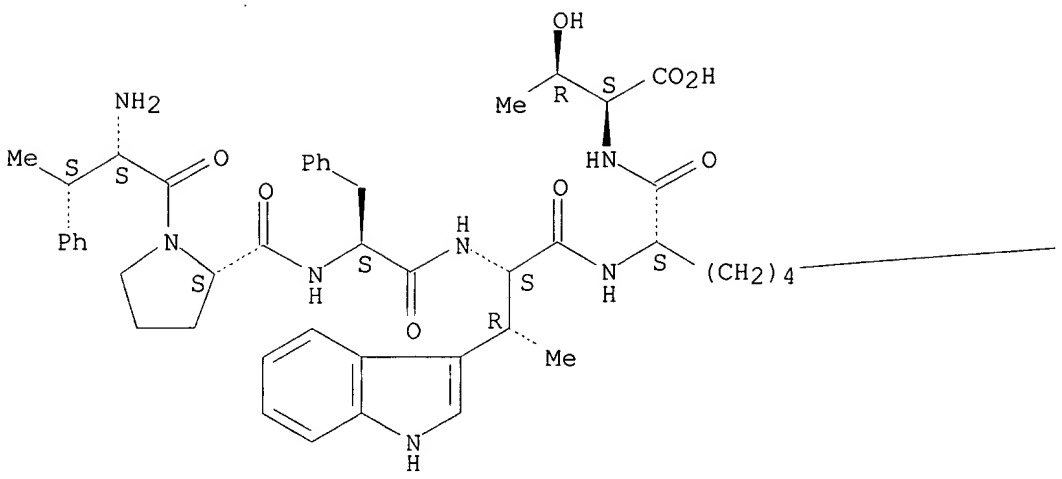
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:316555

L8 ANSWER 6 OF 13 REGISTRY COPYRIGHT 2000 ACS
RN 150805-43-9 REGISTRY
CN L-Threonine, N-[N6-[(9H-fluoren-9-ylmethoxy)carbonyl]-N2-[threo-.beta.-methyl-N-[N-[1-(erythro-.beta.-methyl-L-phenylalanyl)-L-prolyl]-L-phenylalanyl]-L-tryptophyl]-L-lysyl]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C61 H70 N8 O10
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

PAGE 1-A



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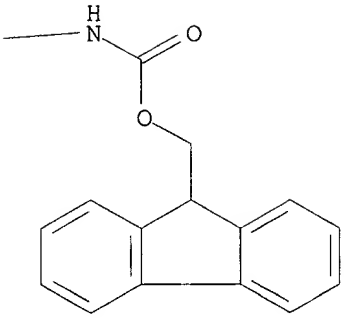


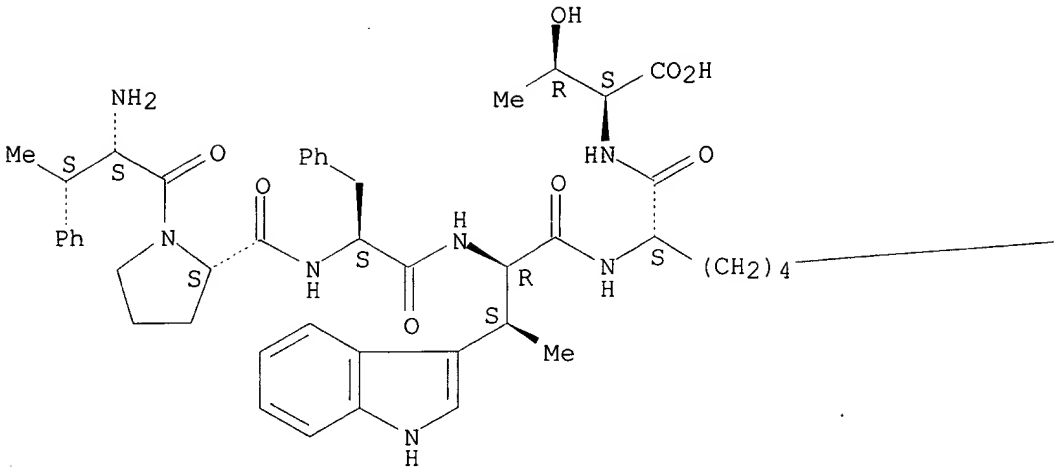
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 119:226393

L8 ANSWER 7 OF 13 REGISTRY COPYRIGHT 2000 ACS
RN 150805-42-8 REGISTRY
CN L-Threonine, N-[N6-[(9H-fluoren-9-ylmethoxy)carbonyl]-N2-[threo-.beta.-methyl-N-[N-[1-(erythro-.beta.-methyl-L-phenylalanyl)-L-prolyl]-L-phenylalanyl]-D-tryptophyl]-L-lysyl]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C61 H70 N8 O10
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

PAGE 1-A



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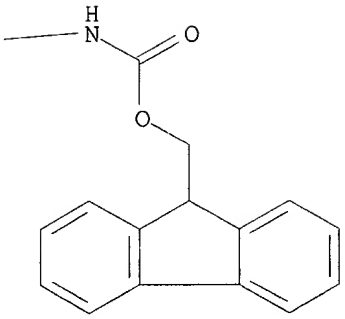


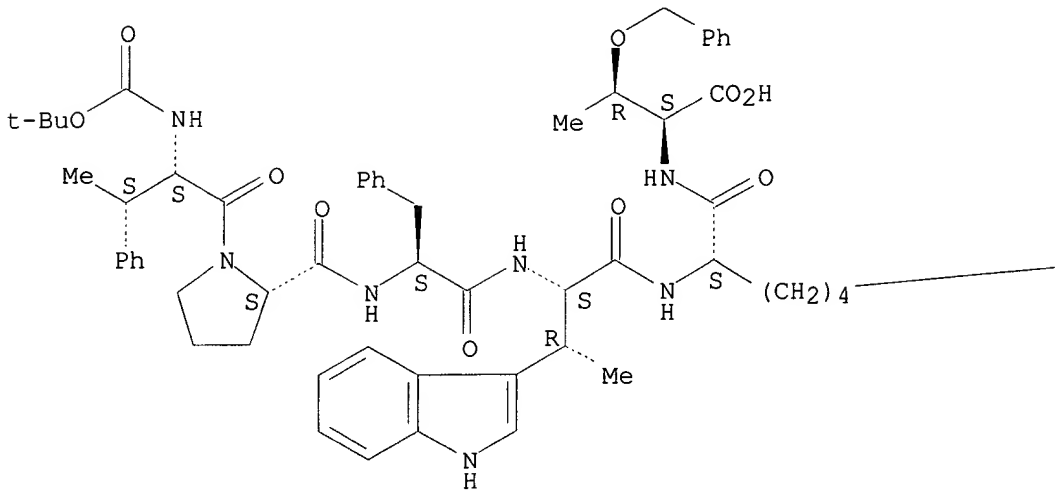
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 119:226393

L8 ANSWER 8 OF 13 REGISTRY COPYRIGHT 2000 ACS
RN 150805-41-7 REGISTRY
CN L-Threonine, N-[N2-[N-[N-[1-[N-[(1,1-dimethylethoxy)carbonyl]-erythro-.beta.-methyl-L-phenylalanyl]-L-prolyl]-L-phenylalanyl]-threo-.beta.-methyl-L-tryptophyl]-N6-[(9H-fluoren-9-ylmethoxy)carbonyl]-L-lysyl]-O-(phenylmethyl)- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C73 H84 N8 O12
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

PAGE 1-A



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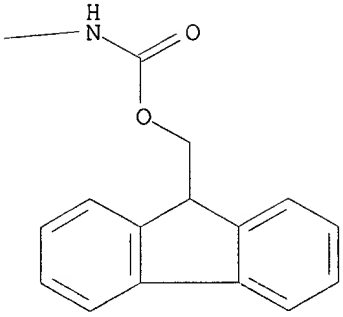

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1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 119:226393

L8 ANSWER 9 OF 13 REGISTRY COPYRIGHT 2000 ACS
RN 150805-40-6 REGISTRY
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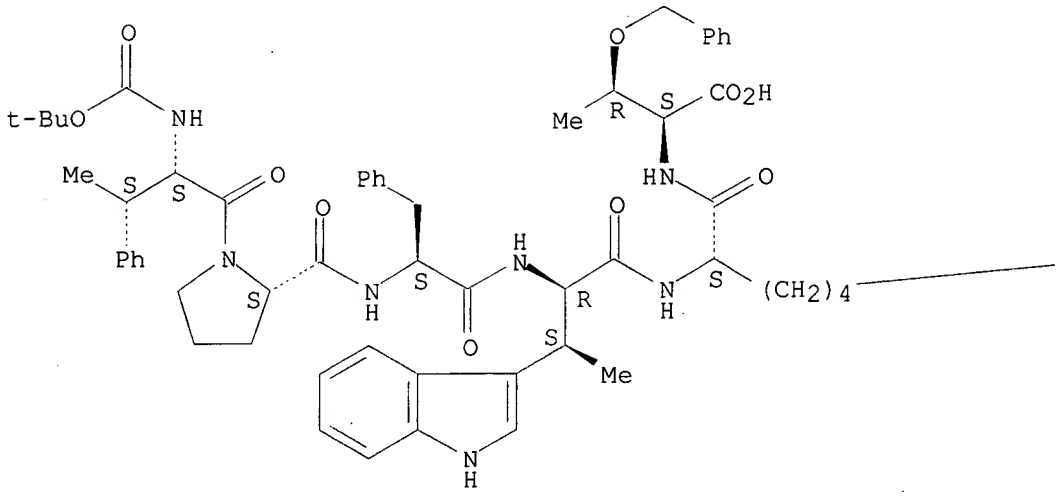
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C73 H84 N8 O12
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

PAGE 1-A



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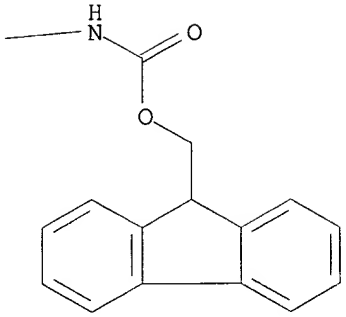

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REFERENCE 1: 119:226393

L8 ANSWER 10 OF 13 REGISTRY COPYRIGHT 2000 ACS
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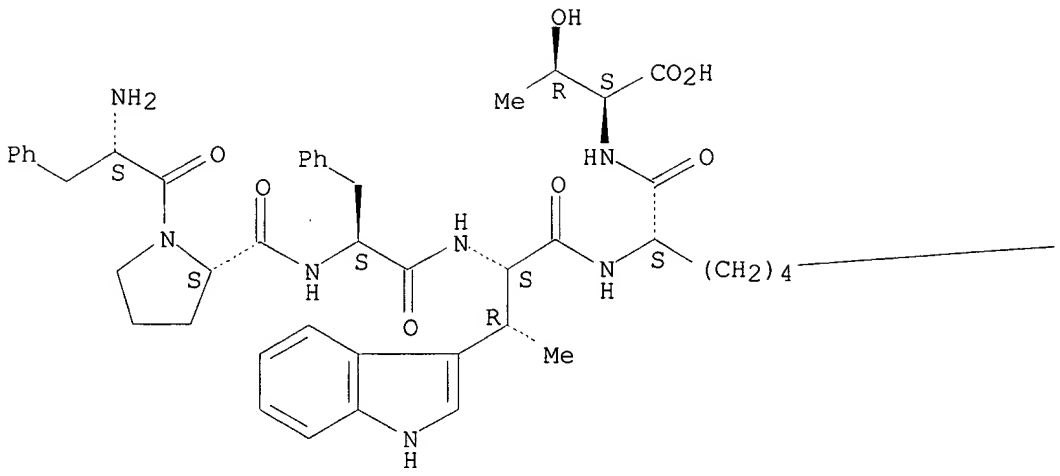
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C60 H68 N8 O10 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 145432-63-9
CMF C60 H68 N8 O10

Absolute stereochemistry.

PAGE 1-A



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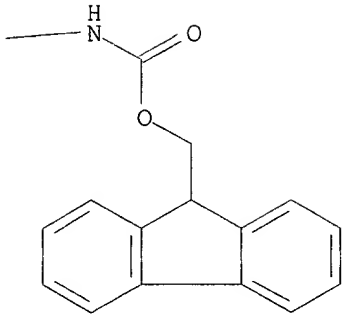

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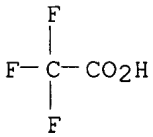

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REFERENCE 1: 118:60082

L8 ANSWER 11 OF 13 REGISTRY COPYRIGHT 2000 ACS
RN 145432-63-9 REGISTRY
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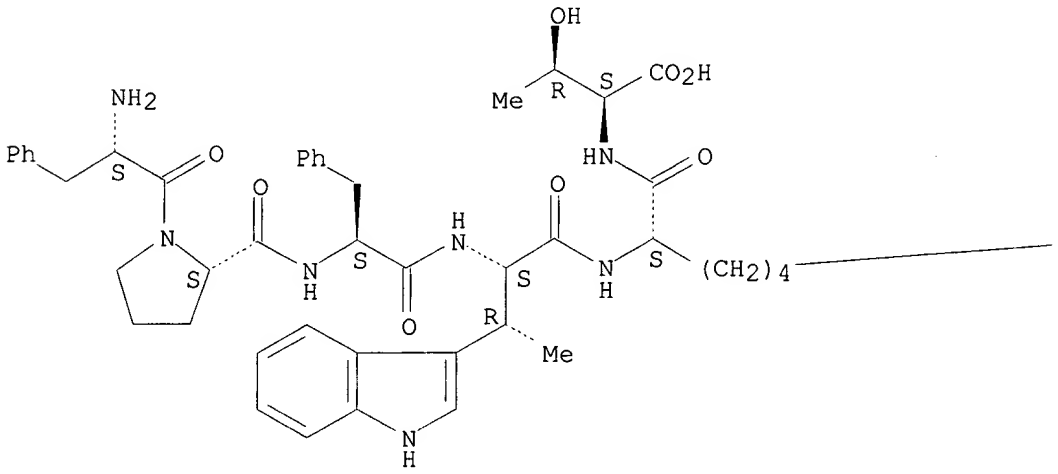
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C60 H68 N8 O10
CI COM
SR CA

Absolute stereochemistry.

PAGE 1-A



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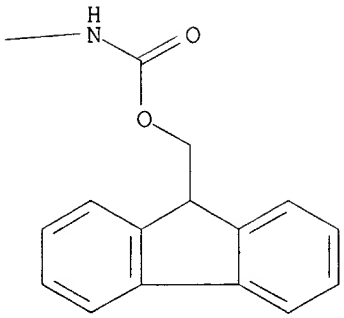

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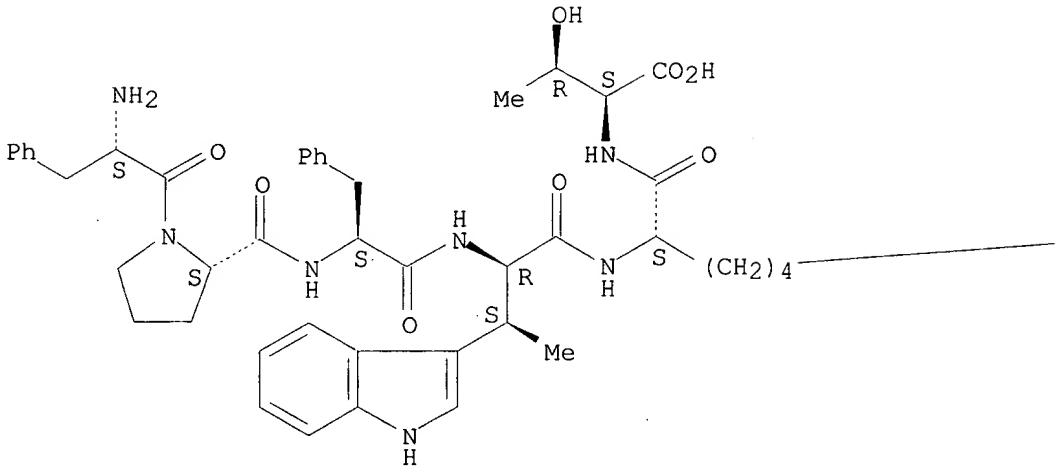
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C60 H68 N8 O10 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS

CM 1

CRN 145432-61-7
CMF C60 H68 N8 O10

Absolute stereochemistry.

PAGE 1-A



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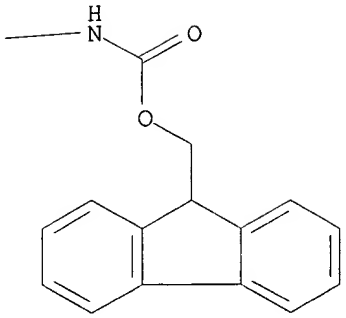

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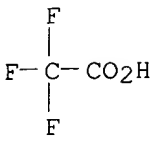

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 118:60082

L8 ANSWER 13 OF 13 REGISTRY COPYRIGHT 2000 ACS
RN 145432-61-7 REGISTRY
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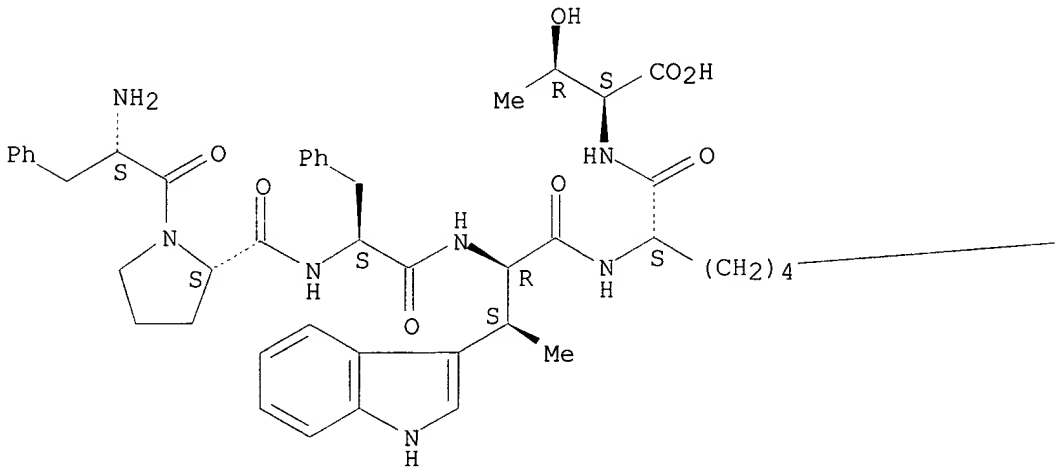
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C60 H68 N8 O10
CI COM
SR CA

Absolute stereochemistry.

PAGE 1-A



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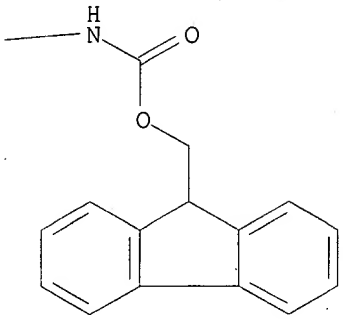

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FILE COVERS 1967 - 7 Feb 2000  VOL ISS 7  ISS ISS
FILE LAST UPDATED: 6 Feb 2000  (20000206/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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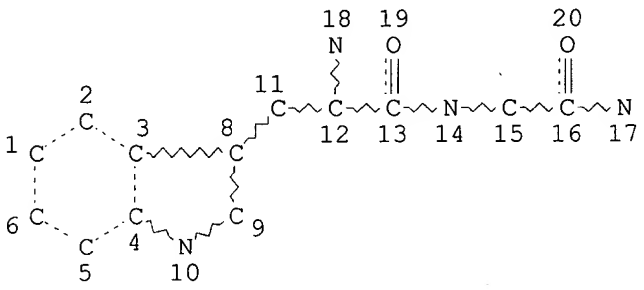


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STEREO ATTRIBUTES: NONE
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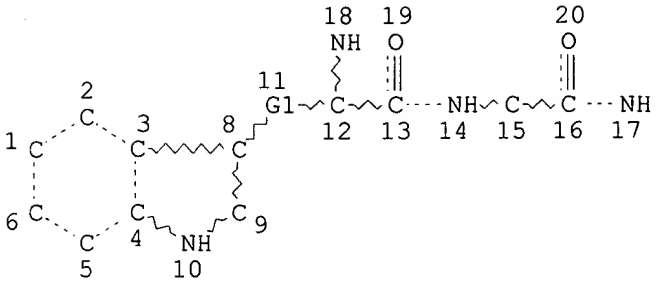

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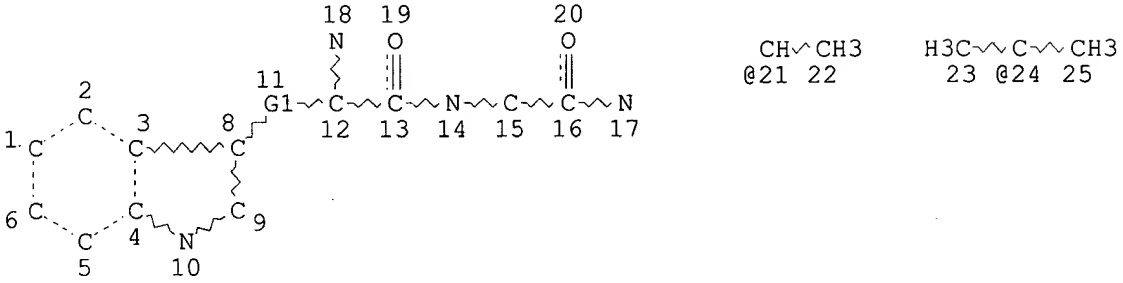

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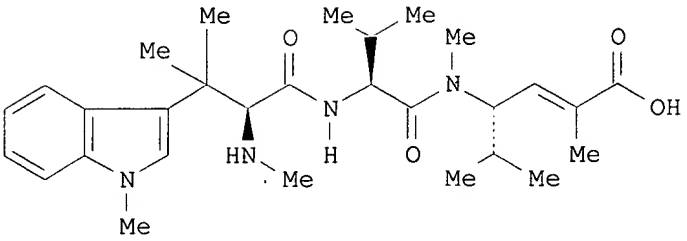
L15  ANSWER 1 OF 14  HCAPLUS  COPYRIGHT 2000 ACS
ACCESSION NUMBER:        1999:636934  HCAPLUS
DOCUMENT NUMBER:         132:167
TITLE:                   Interactions of the Sponge-Derived Antimitotic
                         Tripeptide Hemiasterlin with Tubulin: Comparison with
                         Dolastatin 10 and Cryptophycin 1
AUTHOR(S):               Bai, Ruoli; Durso, Neil A.; Sackett, Dan L.; Hamel,
                         Ernest
CORPORATE SOURCE:        Science Applications International
                         Corporation-Frederick, National Cancer Institute
                         Frederick Cancer Research and Development Center,
                         Frederick, MD, 21702, USA
SOURCE:                  Biochemistry (1999), 38(43), 14302-14310
                         CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER:               American Chemical Society
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   The sponge-derived antimitotic tripeptide hemiasterlin was previously
     shown to inhibit tubulin polymn.  The authors have now demonstrated that
     hemiasterlin resembles most other antimitotic peptides in noncompetitively
     inhibiting the binding of vinblastine to tubulin (apparent Ki value, 7.0
     .mu.M), competitively inhibiting the binding of dolastatin 10 to tubulin
     (apparent Ki value, 2.0 .mu.M), stabilizing the colchicine binding
     activity of tubulin, inhibiting nucleotide exchange on .beta.-tubulin, and
     inducing the formation of tubulin oligomers that are stable to gel
     filtration in the absence of free drug, even at low drug concns.  The
     tubulin oligomerization reaction induced by hemiasterlin was compared to
     the reactions induced by dolastatin 10 and cryptophycin 1.  Like
     dolastatin 10, hemiasterlin induced formation of a tubulin aggregate that
     had the morphol. appearance primarily of ring-like structures with a diam.
     of about 40 nm, while the morphol. of the cryptophycin 1 aggregate
     consisted primarily of smaller rings (diam. about 30 nm).  However, the
     hemiasterlin aggregate differed from the dolastatin 10 aggregate in that
     its formation was not assocd. with turbidity development, and the morphol.
     of the hemiasterlin aggregate (as opposed to the dolastatin 10 aggregate)
     did not change greatly when microtubule-assocd. proteins were present
     (tight coils and pinwheels are obsd. with dolastatin 10 but not with
     hemiasterlin or cryptophycin 1).  Opacification of tubulin-dolastatin 10
     mixts. was inhibited by hemiasterlin at 22.degree. and stimulated at
     0.degree., while cryptophycin 1 was inhibitory at both reaction temps.
IT   157207-90-4, Hemiasterlin
     RL: BAC (Biological activity or effector, except adverse); BIOL
     (Biological study)
        (interactions of sponge-derived antimitotic tripeptide hemiasterlin
        with tubulin and comparison with dolastatin 10 and cryptophycin 1)

L15  ANSWER 2 OF 14  HCAPLUS  COPYRIGHT 2000 ACS
ACCESSION NUMBER:        1999:571349  HCAPLUS
DOCUMENT NUMBER:         131:284111
TITLE:                   Cytotoxic and tubulin-interactive hemiasterlins from
                         Auletta sp. and Siphonochalina spp. sponges
AUTHOR(S):               Gamble, William R.; Durso, Neil A.; Fuller, Richard
                         W.; Westergaard, Chandra K.; Johnson, Tanya R.;
                         Sackett, Dan L.; Hamel, Ernest; Cardellina, John H.,
```

II; Boyd, Michael R.
CORPORATE SOURCE: Laboratory of Drug Discovery Research and Development Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, MD, 21702-1201, USA
SOURCE: Bioorg. Med. Chem. (1999), 7(8), 1611-1615
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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AB Chem. and biol. investigations of exts. from the sponge genus Auletta and 2 collections of Siphonochalina sp. have shown these organisms to be producers of the potent hemiasterlin class of antitumor agents. In addn. to the previously known hemiasterlin and hemiasterlin A, a new analog, hemiasterlin C (I), was isolated and identified. The structures of hemiasterlin and hemiasterlin A were assigned based on comparison to literature values, and I was identified on the basis of 1H NMR, 13C NMR, COSY, HSQC, and HMBC expts. The cytotoxic and anti-tubulin activities of the 3 compds. were evaluated. In a comparative assay for inhibition of tubulin polymn., the hemiasterlins were more potent than dolastatin 15 and equipotent with cryptophycin 1, but were somewhat less potent than dolastatin 10.

IT **246847-61-0P**, Hemiasterlin C
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
(hemiasterlin C isolation, structure, and cytotoxic and tubulin polymn.-inhibiting activity from sponges)

IT **157207-90-4**, Hemiasterlin **169181-24-2**, Hemiasterlin A
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(hemiasterlin C isolation, structure, and cytotoxic and tubulin polymn.-inhibiting activity from sponges)

L15 ANSWER 3 OF 14 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:425787 HCAPLUS
DOCUMENT NUMBER: 131:59140
TITLE: Hemiasterlin analogs
INVENTOR(S): Andersen, Raymond; Piers, Edward; Nieman, James; Coleman, John; Roberge, Michel
PATENT ASSIGNEE(S): The University of British Columbia, Can.
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932509	A2	19990701	WO 1998-CA1184	19981218
WO 9932509	A3	19991007		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: CA 1997-2225325 19971219
OTHER SOURCE(S): MARPAT 131:59140
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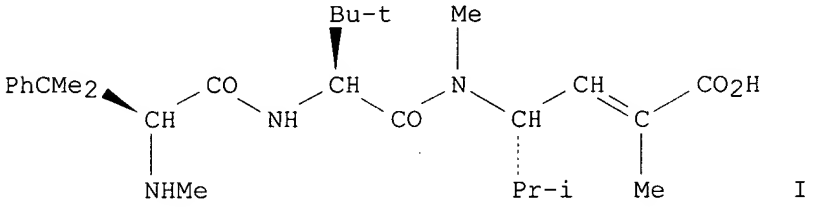

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AB Hemiasterlin analogs R3R4R5CCH(NR1R2)CONR6CHR7CONR8R9 [R1, R2 = H, R, ArR- (R is satd. or unsatd. moiety having a linear, branched, or cyclic skeleton contg. 1-10 (un)substituted carbon atoms, 0-4 nitrogen atoms, 0-4 oxygen atoms, 0-4 sulfur atoms; Ar is an arom. ring) or R1R2N is cyclic amino; R3, R4, R6, R7, R8 = H, R, ArR-; R5 = H, R, ArR-, Ar; R9 = ZCOY- (Y is optionally substituted alkyl; Z = OH, OR, SH, SR, NH2, NHR, NR2, etc.)] were prepd. as cytotoxic and anti-mitotic agents. Thus, peptide I trifluoroacetate, prepd. via peptide coupling in soln., showed higher antimitotic activity than hemiasterlin.

IT **157207-90-4DP**, Hemiasterlin, analogs
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of hemiasterlin analogs)

L15 ANSWER 4 OF 14 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:682382 HCAPLUS
DOCUMENT NUMBER: 129:302887
TITLE: Preparation of tryptophanamides as somatostatin agonists
INVENTOR(S): Yang, Lihu; Patchett, Arthur A.; Pasternak, Alexander; Chapman, Kevin; Tata, James R.; Guo, Liangqin
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 133 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9845285	A1	19981015	WO 1998-US6455	19980402

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RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,

CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9869460	A1	19981030	AU 1998-69460	19980402
PRIORITY APPLN. INFO.:			US 1997-42920	19970404
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			WO 1998-US6455	19980402

OTHER SOURCE(S): MARPAT 129:302887

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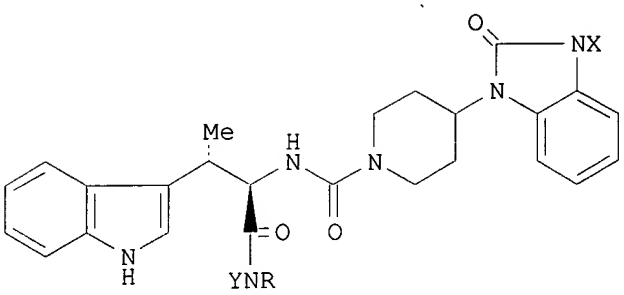


I

AB Title compds. [I; X = H, CH3CH2; Y = H, CH3; R = substituted 3-pyridyl, 4-pyridyl, 2-(4-imidazolyl)ethyl, 2-(4-piperazine)ethyl, substituted 2-dioxanyl, substituted 2-tetrahydrofurylmethyl], pharmaceutically acceptable salts, hydrates are prepd. as Somatostatin agonist useful in the treatment of diabetes, cancer, acromegaly, restenosis, depression, irritable bowel syndrome and pain.

IT **214471-72-4P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of tryptophanamides as somatostatin agonists)

IT **214472-02-3P 214472-04-5P 214472-05-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of tryptophanamides as somatostatin agonists)

L15 ANSWER 5 OF 14 HCAPLUS COPYRIGHT 2000 ACS

ACCESSION NUMBER:	1997:576607 HCAPLUS
DOCUMENT NUMBER:	127:195464
TITLE:	Hemiasterlin and geodiamolide TA from the sponge Hemiasterella minor, and methods using them for treatment of tumors
INVENTOR(S):	Kashman, Yoel; Gravalos, Dolores G.
PATENT ASSIGNEE(S):	Israel
SOURCE:	U.S., 6 pp. CODEN: USXXAM
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5661175	A	19970826	US 1995-492726	19950620

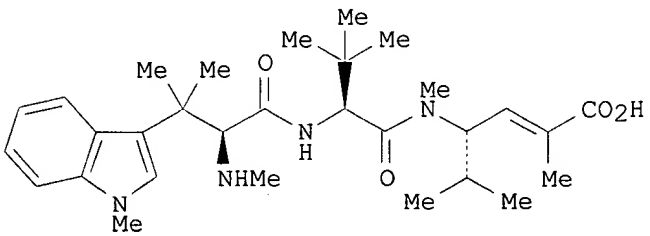
AB Three cytotoxic peptides, the known compd. Jaspamide and two new peptides, hemiasterlin and geodiamolide TA, have been isolated from the sponge Hemiasterella minor. The structures of the three were detd. by interpreting the NMR and mass spectra. Hemiasterlin is a novel linear tripeptide embodying two unique, new natural amino acids and geodiamolide TA is a newly discovered higher homolog of geodiamolides A-F. Also disclosed are methods for treating tumors with the compds. of the invention.

IT **157207-90-4P**, Hemiasterlin
RL: BAC (Biological activity or effector, except adverse); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological

study); PREP (Preparation); USES (Uses)
(hemiasterlin and geodiamolide TA from Hemiasterella minor, and methods using them for treatment of tumors)

L15 ANSWER 6 OF 14 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:262023 HCAPLUS
DOCUMENT NUMBER: 127:431
TITLE: Cytotoxic peptides hemiasterlin, hemiasterlin A, and hemiasterlin B include mitotic arrest and abnormal spindle formation
AUTHOR(S): Anderson, Hilary J.; Coleman, John E.; Andersen, Raymond J.; Roberge, Michel
CORPORATE SOURCE: Dep. Biochemistry Molecular Biology, Univ. British Columbia, Vancouver, BC, V6T 1Z3, Can.
SOURCE: Cancer Chemother. Pharmacol. (1997), 39(3), 223-226
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mechanism of cytotoxicity of the tripeptides hemiasterlin, hemiasterlin A, and B as antitumor drugs were investigated. The peptides induced arrest in mitotic metaphase. Hemiasterlin A produced abnormal mitotic spindles like those produced by the microtubule inhibitors taxol, nocodazol, and vinblastine in low concns. At high concns. hemiasterlin A caused microtubule depolymn. like nocodazole and vinblastine. Thus, hemiasterlins are cytotoxic by inhibiting spindle microtubule dynamics.
IT **157207-90-4**, Hemiasterlin **169181-24-2**, Hemiasterlin A **169181-25-3**, Hemiasterlin B
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cytotoxicity of tripeptides hemiasterlin, hemiasterlin A, and hemiasterlin B as antitumor drugs)

L15 ANSWER 7 OF 14 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:81264 HCAPLUS
DOCUMENT NUMBER: 126:186356
TITLE: Total synthesis of (-)-hemiasterlin, a structurally novel tripeptide that exhibits potent cytotoxic activity
AUTHOR(S): Anderen, Raymond J.; Coleman, John E.; Piers, Edward; Wallace, Debra J.
CORPORATE SOURCE: Dep. CHem. and Oceanography-Earth & Ocean Sci., Univ. British Columbia, Vancouver, BC, V6T 1Z1, Can.
SOURCE: Tetrahedron Lett. (1997), 38(3), 317-320
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The total synthesis of (-)-hemiasterlin (I), a structurally novel, naturally occurring tripeptide that exhibits potent cytotoxic and antimitotic activity against human breast cancer MCF7 cells, is described.
IT **157207-90-4P**, (-)-Hemiasterlin

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(total synthesis of hemiasterlin, a tripeptide with potent cytotoxic activity)

IT **187345-40-0P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(total synthesis of hemiasterlin, a tripeptide with potent cytotoxic activity)

L15 ANSWER 8 OF 14 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:753909 HCAPLUS
DOCUMENT NUMBER: 126:31667
TITLE: Biologically active peptides and compositions and their use
INVENTOR(S): Andersen, Raymond; Coleman, John; De Silva, Dilip; Kong, Fangming; Piers, Edward; Wallace, Debra; Roberge, Michel; Allen, Theresa
PATENT ASSIGNEE(S): University of British Columbia, Can.; University of Alberta; Appledene Limited; Andersen, Raymond; Coleman, John; De Silva, Dilip; Kong, Fangming; Piers, Edward; Wallace, Debra; et al.
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9633211	A1	19961024	WO 1996-GB942	19960422
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
CA 2220021	AA	19961024	CA 1996-2220021	19960422
AU 9653416	A1	19961107	AU 1996-53416	19960422
EP 839154	A1	19980506	EP 1996-910116	19960422
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
JP 11505211	T2	19990518	JP 1996-531564	19960422
PRIORITY APPLN. INFO.:			GB 1995-8195	19950420
			WO 1996-GB942	19960422

OTHER SOURCE(S): MARPAT 126:31667
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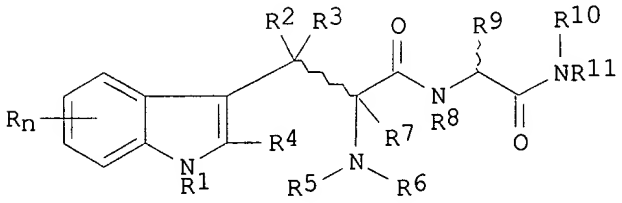

I

AB Hemiasterlin compds. I (Rn = 0-4 substituents, R1, R2, R3, R5, R6 = H, optionally substituted alkyl or acyl, R4 = H or substituent, R7 = H or R3R7 = bond, R8 = H, OH, or optionally substituted alkyl or acyl, R9 = H or optionally substituted alkyl, R10 = H or alkyl, R11 = optionally substituted alkyl) are claimed as medicaments for use in therapy. Thus, hemiasterlin and related compds. were isolated from Cymbastela sp. and their antimitotic activity compared with that of a synthetic analog.

IT **179939-69-6 184434-35-3**

RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(biol. active peptides and compns. and their use)
IT **169181-25-3P**, Hemiasterlin b **169181-27-5P**, Criamide-b
RL: BAC (Biological activity or effector, except adverse); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(biol. active peptides and compns. and their use)
IT **157207-90-4P**, Hemiasterlin **169181-24-2P**, Hemiasterlin a
RL: BAC (Biological activity or effector, except adverse); PUR (Purification or recovery); RCT (Reactant); BIOL (Biological study); PREP (Preparation)
(biol. active peptides and compns. and their use)
IT **169181-26-4P**, Criamide-a
RL: PUR (Purification or recovery); PREP (Preparation)
(biol. active peptides and compns. and their use)
IT **184434-33-1P 184434-34-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(biol. active peptides and compns. and their use)

L15 ANSWER 9 OF 14 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:544116 HCAPLUS
DOCUMENT NUMBER: 125:266140
TITLE: The Use of Topographical Constraints In Receptor Mapping: Investigation of the Topographical Requirements of the Tryptophan 30 Residue for Receptor Binding of Asp-Tyr-D-Phe-Gly-Trp-(N-Me)Nle-Asp-Phe-NH2 (SNF 9007), a Cholecystokinin (26-33) Analog That Binds to both CCK-B and .delta.-Opioid Receptors
AUTHOR(S): Boteju, Lakmal W.; Nikiforovich, Gregory V.; Haskell-Luevano, Carrie; Fang, Su-Nan; Zalewska, Teresa; Stropova, Dagmar; Yamamura, Henry I.; Hruby, Victor J.
CORPORATE SOURCE: Department of Chemistry, University of Arizona, Tucson, AZ, 85721, USA
SOURCE: J. Med. Chem. (1996), 39(20), 4120-4124
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cholecystokinin (26-33) [CCK (26-33)] octapeptide analog Asp-Tyr-D-Phe-Gly-Trp(N-Me)Nle-Asp-Phe-NH2 (SNF 9007) is a potent and selective ligand for both the CCK-B and .delta.-opioid receptors. Pharmacol. studies of SNF 9007 suggest a relation between the ligand requirements of CCK-B and .delta.-opioid receptors, which further implies a possible structural relation between these receptors. We have utilized topog. constrainment of the important Trp30 residue to investigate structural features of SNF 9007 that would distinguish between binding requirements in this region for the CCK-B and .delta.-opioid receptors. Thus, the four optically pure isomers of .beta.-MeTrp were substituted for L-Trp30 of SNF 9007. Receptor binding results suggest that the preferred topog. of the Trp30 residue for CCK-B receptor binding may be the 2S,3S (erythro-L) configuration whereas for the .delta.-opioid receptor it may be the 2S,3R (threo-L) configuration. Mol. modeling studies of these ligands further support the recently revised receptor-bound model for CCK-B octapeptide ligands (S. A. Kolodziej et al., 1995) and are in good agreement with the DPDPE-.delta. opioid receptor "template" model (G. V. Nikiforovich, et al., 1991).
IT **166255-35-2 166255-36-3 166255-37-4 166255-38-5**
RL: BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(SNF 9007 and SNF 9007 methyltryptophan isomers topol. constraints in binding to both CCK-B and .delta.-opioid receptors)

L15 ANSWER 10 OF 14 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1996:403658 HCAPLUS
DOCUMENT NUMBER: 125:143286

TITLE: Hemiasterlin methyl ester
AUTHOR(S): Coleman, John E.; Patrick, Brian O.; Andersen, Raymond J.; Rettig, Steven J.
CORPORATE SOURCE: Dep. Chemistry, Univ. British Columbia, Vancouver, BC, V6T 1Z1, Can.
SOURCE: Acta Crystallogr., Sect. C: Cryst. Struct. Commun. (1996), C52(6), 1525-1527
CODEN: ACSCEE; ISSN: 0108-2701
DOCUMENT TYPE: Journal
LANGUAGE: English
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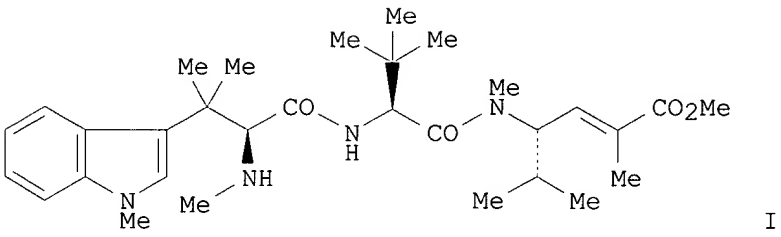


I

AB The structure of the tripeptide hemiasterlin Me ester I was detd. by x-ray anal. The abs. configuration is based on the chiralities detd. by other methods for two of the three chiral centers. Weak hydrogen bonding influences the solid state conformation.
IT **157207-90-4**, Hemiasterlin
RL: PRP (Properties); RCT (Reactant)
(crystal structure and abs. configuration of hemiasterlin Me ester)
IT **179939-69-6P**, Hemiasterlin methyl ester
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(crystal structure and abs. configuration of hemiasterlin Me ester)

L15 ANSWER 11 OF 14 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:836608 HCAPLUS
DOCUMENT NUMBER: 123:251821
TITLE: Cytotoxic peptides from the marine sponge Cymbastela sp.
AUTHOR(S): Coleman, John E.; de Silva, E. Dilip; Kong, Fangming; Andersen, Raymond J.; Allen, Theresa M.
CORPORATE SOURCE: Dep. Chemistry, Univ. British Columbia, Vancouver, BC, V6T 1Z4, Can.
SOURCE: Tetrahedron (1995), 51(39), 10653-62
CODEN: TETRAB; ISSN: 0040-4020
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

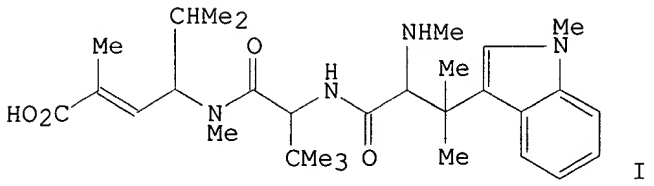
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Exts. of the sponge Cymbastela sp. have yielded the novel cytotoxic peptides geodiamolide G (I), hemiasterlin A and hemiasterlin B with a general structure of (II), criamide A and criamide B with a general structure of (III). The structures of the new compds. were solved via spectroscopic anal. and chem. degrdn.
IT **169181-24-2**, Hemiasterlin A **169181-25-3**, Hemiasterlin B
169181-26-4, Criamide A **169181-27-5**, Criamide B
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(peptide isolation and structural characterization and cytotoxic activity from marine sponge)

IT **157207-90-4**, Hemiasterlin
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(peptide isolation and structural characterization and cytotoxic activity from marine sponge)

L15 ANSWER 12 OF 14 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:498904 HCAPLUS
DOCUMENT NUMBER: 123:112674
TITLE: Facile removal of the N-indole-mesitylenesulfonyl protecting group using HF cleavage conditions
AUTHOR(S): Haskell-Luevano, Carrie; Boteju, Lakmal W.; Hruby, Victor J.
CORPORATE SOURCE: Department of Chemistry, University of Arizona, Tucson, AZ, 85721, USA
SOURCE: Lett. Pept. Sci. (1995), 1(4), 163-70
CODEN: LPSCEM; ISSN: 0929-5666
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nitrogen indole protection of the .beta.-methyltryptophan side chain is important for avoiding undesired side reactions during peptide synthesis. Of great importance is the choice of a side chain protecting group for orthogonal peptide synthesis and its stability under a variety of chem. conditions required for synthesis of the four isomers of this unusual amino acid. The authors report here the successful use of the mesitylenesulfonyl (Mts) protecting group for .beta.-methyltryptophan in the synthesis of melanotropin and cholecystokinin (CCK) peptide analogs and the ready cleavage of this protecting group under HF conditions.
IT **166255-35-2P 166255-36-3P 166255-37-4P 166255-38-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(facile removal of tryptophan indole mesitylenesulfonyl protecting groups using HF)

L15 ANSWER 13 OF 14 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1994:530293 HCAPLUS
DOCUMENT NUMBER: 121:130293
TITLE: Hemiasterlin and geodiamolide TA; two new cytotoxic peptides from the marine sponge Hemiasterella minor (Kirkpatrick)
AUTHOR(S): Talpir, R.; Benayahu, Y.; Kashman, Y.; Pannell, L.; Schleyer, M.
CORPORATE SOURCE: Sch. Chem. Dep. Zoology, Tel Aviv Univ., Tel Aviv, 69978, Israel
SOURCE: Tetrahedron Lett. (1994), 35(25), 4453-6
CODEN: TELEAY; ISSN: 0040-4039
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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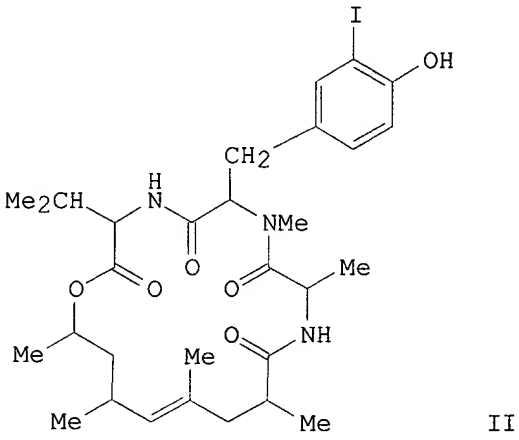

II

AB Three cytotoxic peptides, Jaspamide and the 2 new peptides hemiasterlin (I) and geodiamolide TA (II), were isolated from the sponge H. minor. The structures were detd. by interpretating the NMR and mass spectra. I is a novel linear tripeptide embodying 2 unique, new natural amino acids and II is a higher homolog of geodiamolides A-F.

IT **157207-90-4**, Hemiasterlin
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(of marine sponge, isolation and mol. structure and cytotoxic activity of)

L15 ANSWER 14 OF 14 HCAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1979:421053 HCAPLUS
DOCUMENT NUMBER: 91:21053
TITLE: Fluorescence study of A-128-OP antibiotic
AUTHOR(S): Minaev, V. E.; Smirnova, I. G.; Sergeev, G. B.; Katrukha, G. S.; Silaev, A. B.
CORPORATE SOURCE: Khim. Fak., Mosk. Gos. Univ., Moscow, USSR
SOURCE: Deposited Doc. (1977), VINITI 2778-77, 14 pp. Avail.: VINITI
DOCUMENT TYPE: Report
LANGUAGE: Russian

AB UV and fluorescence spectra were detd. for antibiotic A-128-OP (I), antibiotic A-128-OP acid, .beta.-methyltryptophan, and N-benzoyldehydrotryptophylglycine. Calcns. based on the induction-resonance theory of energy transfer in fluorescence showed that breaking the ester bond in I increased the distance between the methyltryptophan and dehydrotryptophan moieties and weakened interactions between them.

IT **70569-55-0**
RL: PRP (Properties)
(fluorescence spectrum of, mol. structure in relation to)

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DICTIONARY FILE UPDATES: 4 FEB 2000 HIGHEST RN 254912-96-4

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 13, 1999

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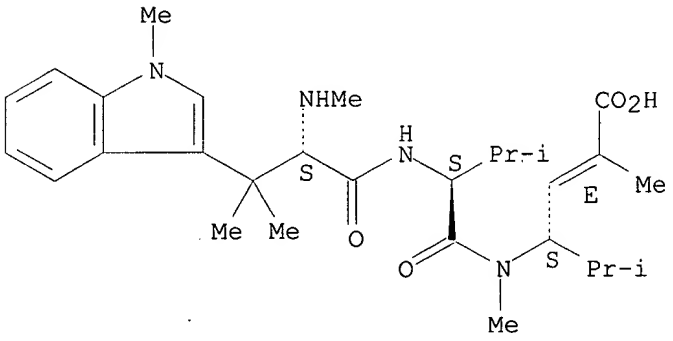
L13 ANSWER 1 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 246847-61-0 REGISTRY
CN L-Valinamide, N,.beta.,.beta.,1-tetramethyl-L-tryptophyl-N-[(1S,2E)-3-carboxy-1-(1-methylethyl)-2-butenyl]-N-methyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Hemiasterlin C
FS STEREOSEARCH
MF C29 H44 N4 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.

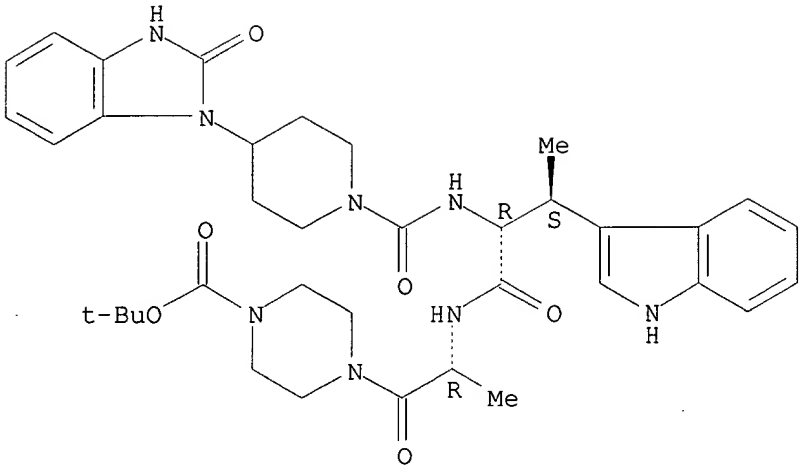


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:284111

L13 ANSWER 2 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 214472-05-6 REGISTRY
CN 1-Piperazinecarboxylic acid, 4-[(.beta.S)-N-[[4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]carbonyl]-.beta.-methyl-D-tryptophyl-D-alanyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C37 H48 N8 O6
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

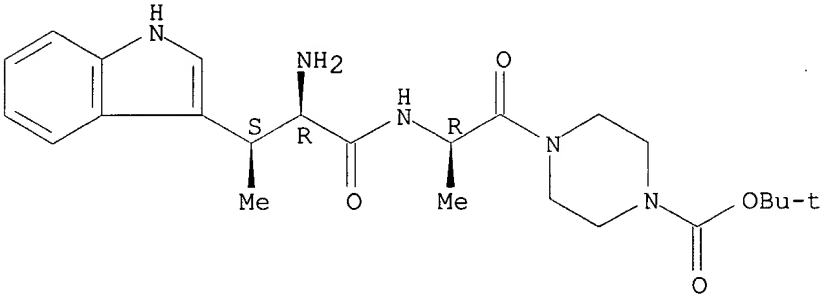


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:302887

L13 ANSWER 3 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 214472-04-5 REGISTRY
CN 1-Piperazinecarboxylic acid, 4-[(.beta.S)-.beta.-methyl-D-tryptophyl-D-alanyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H35 N5 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

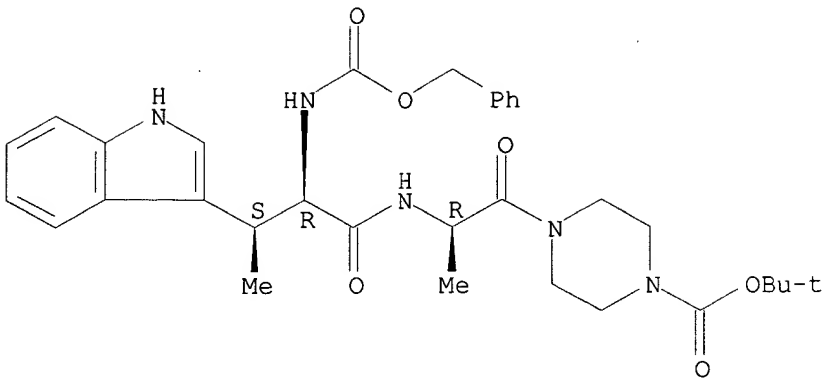


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:302887

L13 ANSWER 4 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 214472-02-3 REGISTRY
CN 1-Piperazinecarboxylic acid, 4-[(.beta.S)-.beta.-methyl-N-[(phenylmethoxy)carbonyl]-D-tryptophyl-D-alanyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C32 H41 N5 O6
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

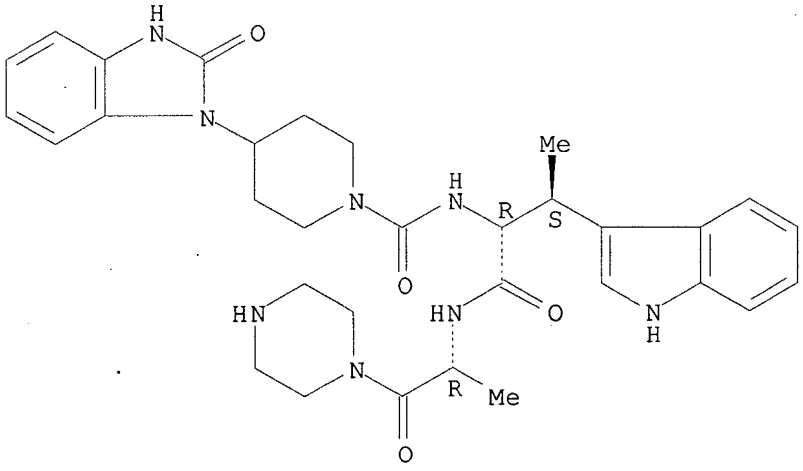


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:302887

L13 ANSWER 5 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 214471-72-4 REGISTRY
CN 1H-Indole-3-propanamide, .alpha.-[[[4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-1-piperidinyl]carbonyl]amino]-.beta.-methyl-N-[(1R)-1-methyl-2-oxo-2-(1-piperazinyl)ethyl]-, monohydrochloride, (.alpha.R,.beta.S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C32 H40 N8 O4 . Cl H
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



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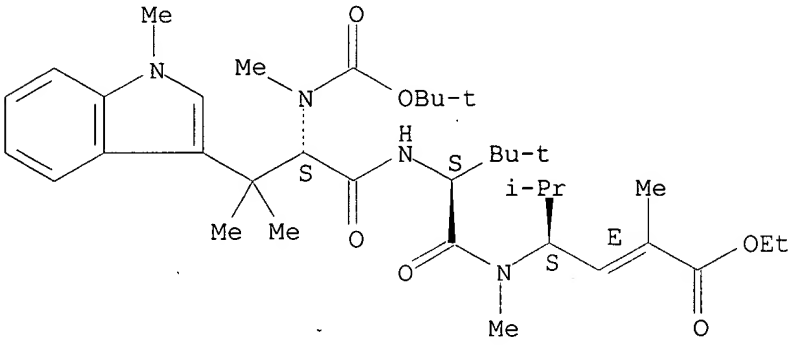
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:302887

L13 ANSWER 6 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 187345-40-0 REGISTRY

CN L-Valinamide, N-[(1,1-dimethylethoxy)carbonyl]-N,.beta.,.beta.,1-tetramethyl-L-tryptophyl-N,3-dimethyl-N-[(1S,2E)-4-ethoxy-3-methyl-1-(1-methylethyl)-4-oxo-2-butenyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C37 H58 N4 O6
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.
Double bond geometry as shown.

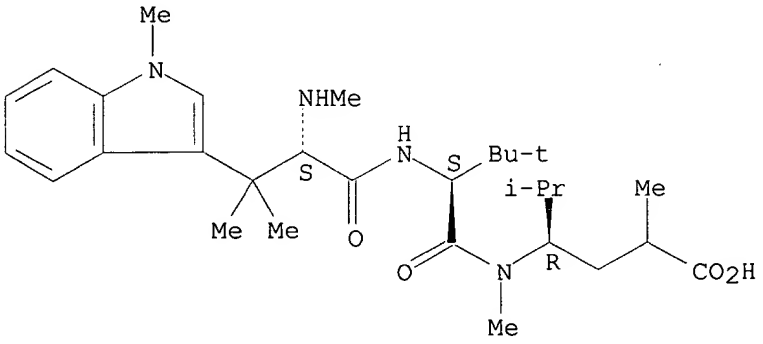


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:186356

L13 ANSWER 7 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 184434-35-3 REGISTRY
CN L-Valinamide, N,.beta.,.beta.,1-tetramethyl-L-tryptophyl-N-[(1R)-3-carboxy-1-(1-methylethyl)butyl]-N,3-dimethyl- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H48 N4 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



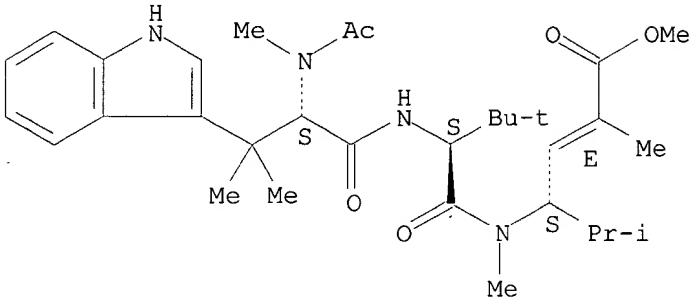
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:31667

L13 ANSWER 8 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 184434-34-2 REGISTRY
CN L-Valinamide, N-acetyl-N,.beta.,.beta.-trimethyl-L-tryptophyl-N-[(1S,2E)-4-methoxy-3-methyl-1-(1-methylethyl)-4-oxo-2-butenyl]-N,3-dimethyl- (9CI) (CA INDEX NAME)
FS STEREOSEARCH

MF C32 H48 N4 O5
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.
Double bond geometry as shown.

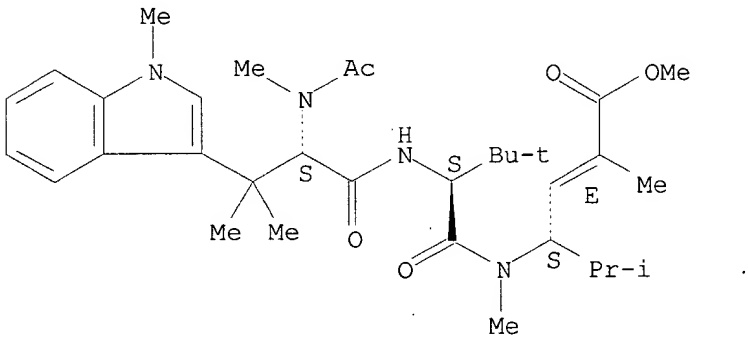


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:31667

L13 ANSWER 9 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 184434-33-1 REGISTRY
CN L-Valinamide, N-acetyl-N,.beta.,.beta.,1-tetramethyl-L-tryptophyl-N-[(1S,2E)-4-methoxy-3-methyl-1-(1-methylethyl)-4-oxo-2-butenyl]-N,3-dimethyl- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C33 H50 N4 O5
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.
Double bond geometry as shown.



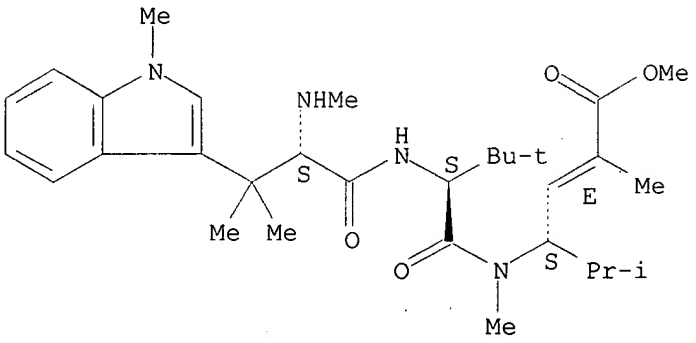
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:31667

L13 ANSWER 10 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 179939-69-6 REGISTRY
CN L-Valinamide, N,.beta.,.beta.,1-tetramethyl-L-tryptophyl-N-[(1S,2E)-4-methoxy-3-methyl-1-(1-methylethyl)-4-oxo-2-butenyl]-N,3-dimethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Valinamide, N,.beta.,.beta.,1-tetramethyl-L-tryptophyl-N-[4-methoxy-3-methyl-1-(1-methylethyl)-4-oxo-2-butenyl]-N,3-dimethyl-, [S-(E)]-
OTHER NAMES:

CN Hemiasterlin methyl ester
FS STEREOSEARCH
MF C31 H48 N4 O4
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.
Double bond geometry as shown.



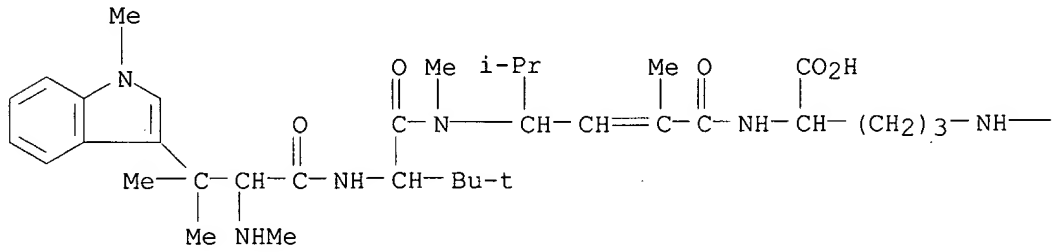
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:31667

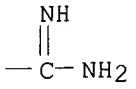
REFERENCE 2: 125:143286

L13 ANSWER 11 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 169181-27-5 REGISTRY
CN L-Valinamide, N,.beta.,.beta.,1-tetramethyltryptophyl-3-methyl-L-valyl-(2E,4S)-2,5-dimethyl-4-(methylamino)-2-hexenoyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Valinamide, N,.beta.,.beta.,1-tetramethyltryptophyl-N-[4-[[4-[(aminoiminomethyl)amino]-1-carboxybutyl]amino]-3-methyl-1-(1-methylethyl)-4-oxo-2-butenyl]-N,3-dimethyl-, [S-[R*,R*-(E)]]-
OTHER NAMES:
CN Criamide B
FS PROTEIN SEQUENCE
MF C36 H58 N8 O5
SR CA
LC STN Files: CA, CAPLUS

PAGE 1-A



PAGE 1-B



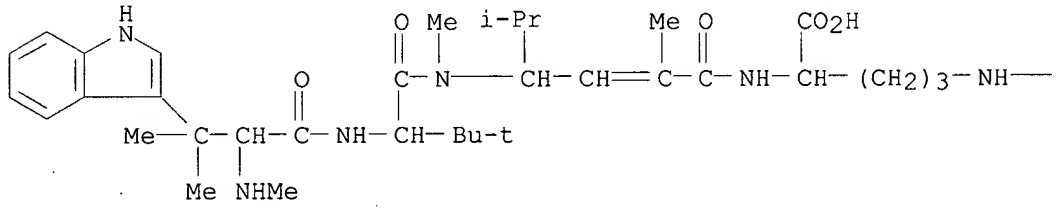
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:31667

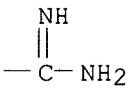
REFERENCE 2: 123:251821

L13 ANSWER 12 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 169181-26-4 REGISTRY
CN L-Arginine, N,.beta.,.beta.-trimethyltryptophyl-3-methyl-L-valyl-(2E,4S)-2,5-dimethyl-4-(methylamino)-2-hexenoyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Valinamide, N,.beta.,.beta.-trimethyltryptophyl-N-[4-[[4-[(aminoiminomethyl)amino]-1-carboxybutyl]amino]-3-methyl-1-(1-methylethyl)-4-oxo-2-butenyl]-N,3-dimethyl-, [S-[R*,R*-(E)]]-
OTHER NAMES:
CN Criamide A
FS PROTEIN SEQUENCE
MF C35 H56 N8 O5
SR CA
LC STN Files: CA, CAPLUS

PAGE 1-A



PAGE 1-B



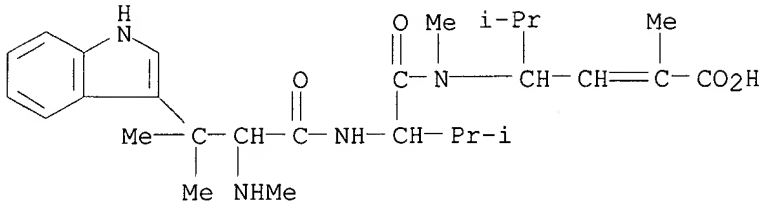
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:31667

REFERENCE 2: 123:251821

L13 ANSWER 13 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 169181-25-3 REGISTRY
CN L-Valinamide, N,.beta.,.beta.-trimethyltryptophyl-N-[(1S,2E)-3-carboxy-1-(1-methylethyl)-2-butenyl]-N-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Valinamide, N,.beta.,.beta.-trimethyltryptophyl-N-[3-carboxy-1-(1-methylethyl)-2-butenyl]-N-methyl-, [S-(E)]-

OTHER NAMES:
CN Hemiasterlin B
MF C28 H42 N4 O4
SR CA
LC STN Files: CA, CAPLUS, TOXLIT



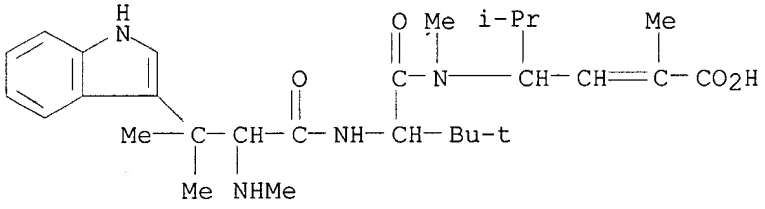
3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:431

REFERENCE 2: 126:31667

REFERENCE 3: 123:251821

L13 ANSWER 14 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 169181-24-2 REGISTRY
CN L-Valinamide, N,.beta.,.beta.-trimethyltryptophyl-N-[(1S,2E)-3-carboxy-1-(1-methylethyl)-2-butenyl]-N,3-dimethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Valinamide, N,.beta.,.beta.-trimethyltryptophyl-N-[3-carboxy-1-(1-methylethyl)-2-butenyl]-N,3-dimethyl-, [S-(E)]-
OTHER NAMES:
CN Hemiasterlin A
MF C29 H44 N4 O4
SR CA
LC STN Files: CA, CAPLUS, TOXLIT



4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:284111

REFERENCE 2: 127:431

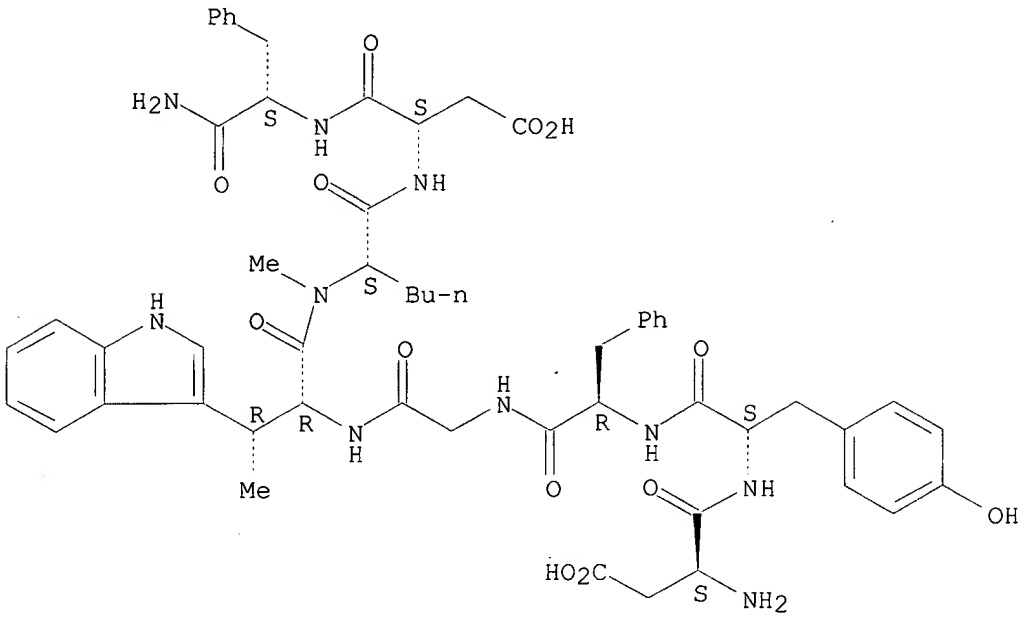
REFERENCE 3: 126:31667

REFERENCE 4: 123:251821

L13 ANSWER 15 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 166255-38-5 REGISTRY
CN L-Phenylalaninamide, L-.alpha.-aspartyl-L-tyrosyl-D-phenylalanylglycyl-erythro-.beta.-methyl-D-tryptophyl-N-methyl-L-norleucyl-L-.alpha.-aspartyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C56 H68 N10 O13

SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry. Rotation (-).



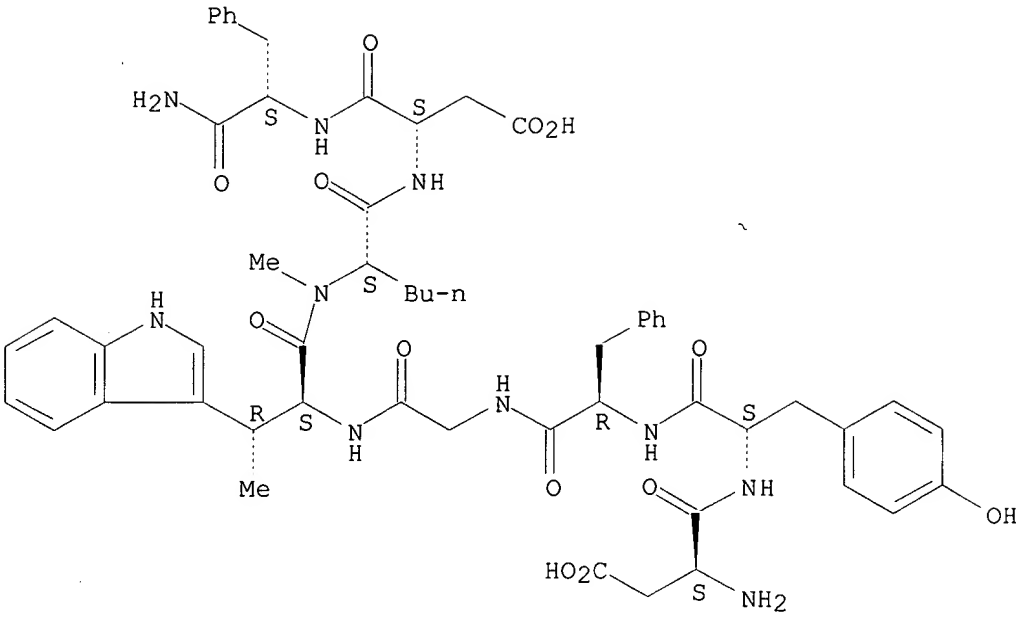
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 125:266140

REFERENCE 2: 123:112674

L13 ANSWER 16 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 166255-37-4 REGISTRY
CN 3-10-Caerulein, 4-desulfo-5-D-phenylalanine-7-(threo-.beta.-methyl-L-tryptophan)-8-(N-methyl-L-norleucine)- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C56 H68 N10 O13
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry. Rotation (-).



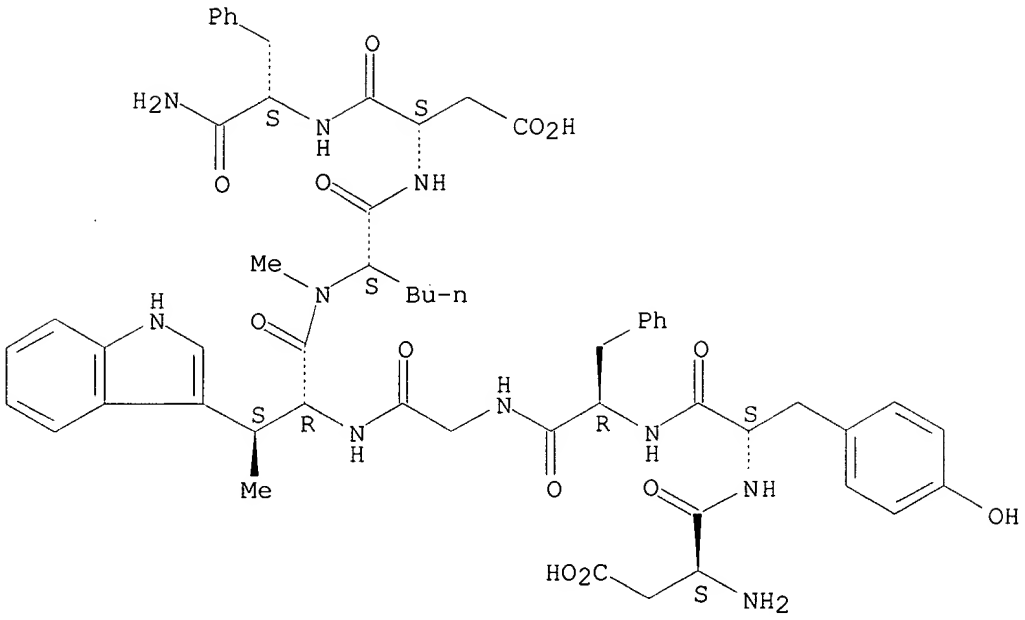
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 125:266140

REFERENCE 2: 123:112674

L13 ANSWER 17 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 166255-36-3 REGISTRY
CN L-Phenylalaninamide, L-.alpha.-aspartyl-L-tyrosyl-D-phenylalanylglycyl-threo-.beta.-methyl-D-tryptophyl-N-methyl-L-norleucyl-L-.alpha.-aspartyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C56 H68 N10 O13
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry. Rotation (-).



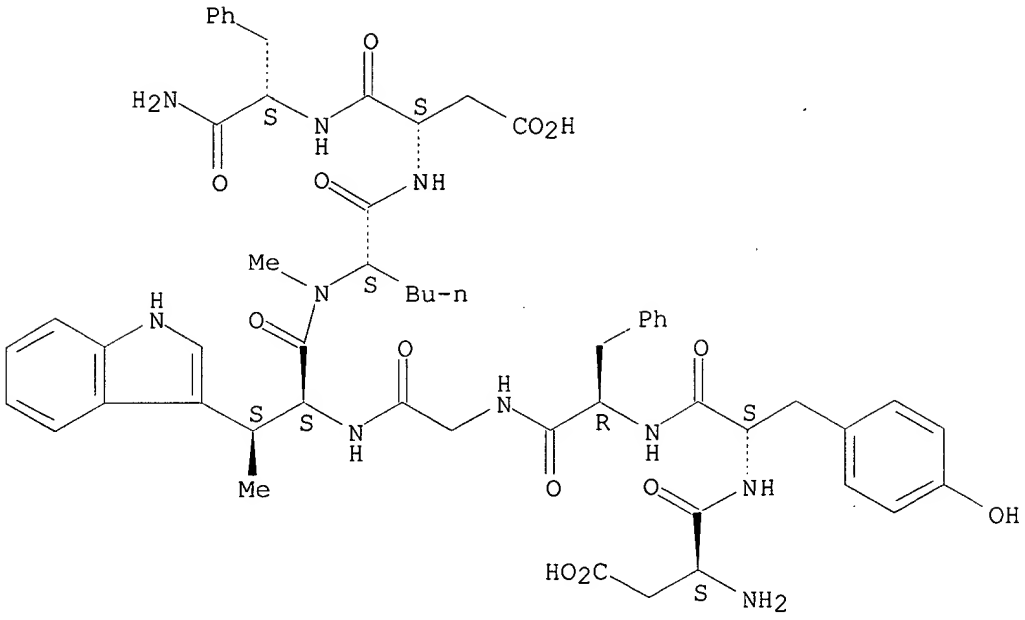
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 125:266140

REFERENCE 2: 123:112674

L13 ANSWER 18 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 166255-35-2 REGISTRY
CN 3-10-Caerulein, 4-desulfo-5-D-phenylalanine-7-(erythro-.beta.-methyl-L-tryptophan)-8-(N-methyl-L-norleucine)- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C56 H68 N10 O13
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry. Rotation (-).



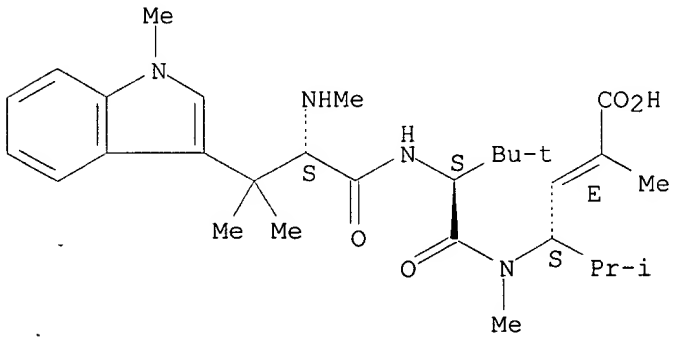
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 125:266140

REFERENCE 2: 123:112674

L13 ANSWER 19 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 157207-90-4 REGISTRY
CN L-Valinamide, N,.beta.,.beta.,1-tetramethyl-L-tryptophyl-N-[(1S,2E)-3-carboxy-1-(1-methylethyl)-2-butenyl]-N,3-dimethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Valinamide, N,.beta.,.beta.,1-tetramethyl-L-tryptophyl-N-[3-carboxy-1-(1-methylethyl)-2-butenyl]-N,3-dimethyl-, [S-(E)]-
OTHER NAMES:
CN (-)-Hemiasterlin
CN Hemiasterlin
FS STEREOSEARCH
MF C30 H46 N4 O4
SR CA
LC STN Files: BIOBUSINESS, CA, CAPLUS, TOXLIT, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.



10 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

10 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:167

REFERENCE 2: 131:284111

REFERENCE 3: 131:59140

REFERENCE 4: 127:195464

REFERENCE 5: 127:431

REFERENCE 6: 126:186356

REFERENCE 7: 126:31667

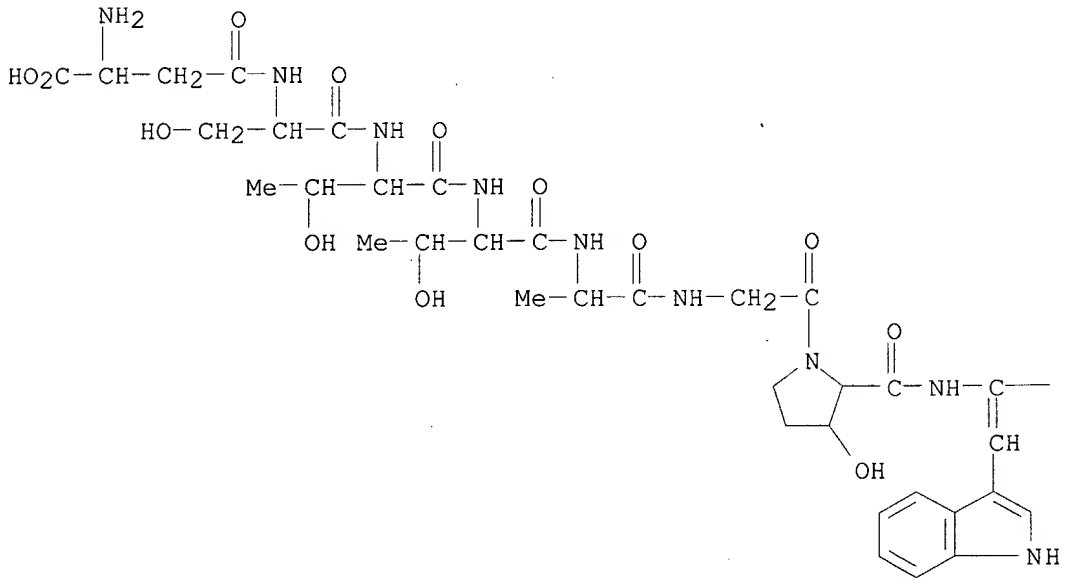
REFERENCE 8: 125:143286

REFERENCE 9: 123:251821

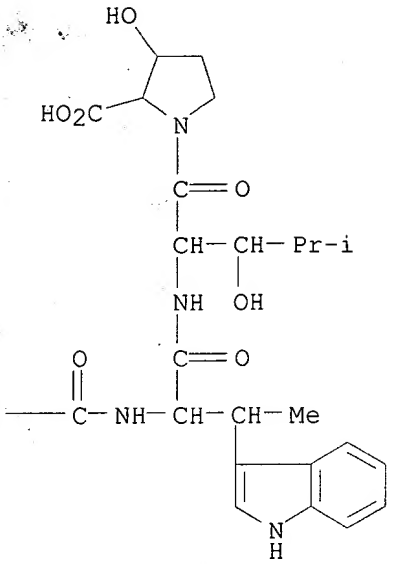
REFERENCE 10: 121:130293

L13 ANSWER 20 OF 20 REGISTRY COPYRIGHT 2000 ACS
RN 70569-55-0 REGISTRY
CN Proline, 1-[N-[N-[N-[1-[N-[N-[N-[N-(N-.beta.-aspartylseryl)threonyl]threonyl]alanyl]glycyl]-3-hydroxyprolyl]-.alpha.,.beta.-didehydrotryptophyl]-.beta.-methyltryptophyl]-3-hydroxyleucyl]-3-hydroxy- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE
MF C59 H79 N13 O20
LC STN Files: CA, CAPLUS

PAGE 1-A



PAGE 1-B



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 91:21053